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SUBACUTE BACTERIAL ENDOCARDITIS

Experiences During the Past Decade

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THE PURPOSE of this paper is to present experience with subacute bacterial endocarditis as it was encountered at the University Hospital, Ann Arbor, Mich., from June 1934 to May 1945. This period begins at a time when no effective treatment was available for this disease, includes the advent of sulfonamide therapy and the more frequently successful combination of sulfonamide compounds with fever induced by administering bacterial vaccine made from the typhoid bacillus, U. S. P., and closes with the effective use of penicillin, resulting in the recovery of the majority of the patients.

The case records have been grouped according to the type of therapy used. In addition, they have been analyzed in regard to the occurrence of the various important features of the disease. In some instances the difference in the frequency of common findings from that reported by others may be significant.

All patients observed during this period for whom the diagnosis of subacute bacterial endocarditis was clearly established are included in this study. No patient is included if the diagnosis was in doubt or if there was failure to obtain a positive blood culture, unless the presence of the disease was demonstrated at autopsy. There were 165 patients, of whom 58 came to autopsy. Prior to 1942 patients with subacute bacterial endocarditis were cared for by the general medical service; from 1942 to 1945 the treatment of these patients was directed by me. This permitted better evaluation of the methods employed. Follow-up data were obtained on all but 5 of the 165 patients.

CLINICAL FEATURES OF THE DISEASE

The common clinical features of subacute bacterial endocarditis as encountered in this series are presented in table 1. Similar data reported by Libman and Friedberg[1] are given for comparison. The present series reveals a lower incidence of petechiae, Osler's nodes,

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1. Libman, E., and Friedberg, C. K.: Subacute Bacterial Endocarditis, New York, Oxford University Press, 1941.

palpable spleen and clubbing of the fingers. There are several explanations for this. Some of the patients were under observation for only a short time and at a period in the illness when some of the well known features of the disease were not present. In addition, it is likely that in recent years the diagnosis of subacute bacterial endocarditis has been made much earlier in the course of the disease, and when therapy is instituted many toxic manifestations of the process are lessened. When patients were subjected to therapy which in itself might account for such manifestations as hematuria and albuminuria, only the conditions present prior to such therapy were included in the analysis. It is

TABLE 1.—*Essential Clinical Features of Subacute Bacterial Endocarditis in One Hundred and Sixty-Five Patients*

Clinical Features	Frequency in This Series, per Cent	Frequency According to Libman and Friedberg [1]
Palpable spleen	46.6	80-90%
Retinitis	20.2	Often
Osler's nodes	28.2	50%
Petechiae	54.0	80%
Janeway's spots	4.3	
Clubbing of fingers	37.4	68%
Embolic phenomena	57.7	
Pallor	52.1	Almost constant
Fever	99.4	Constant
Oral sepsis	42.3	
Hematuria *	40.7	
Albuminuria *	45.3	Almost invariably present
Normal urine *	38.4	
Phagocytic endothelial cells	6.0	Not usually present
Acute embolic onset	6.7	
Auricular fibrillation	1.8	0.9% (1 in 109)
Apparent direct relation to exodontia	13.3	
Apparent direct relation to abortion or puerperium	8.2	

	0-5,000	5,001-10,000	10,001-15,000	15,001-20,000	20,001+
White blood cell count	3.1%	53.4%	30.4%	8.1%	5.0%
	0 M-2.50 M †	2.51 M-4.00 M	4.01 M-6.00 M+		
Red blood cell count...	10.2%	59.8%	30%		

* The specimens of urine were from male patients only.

† "M" means millions.

also true that the appearance of petechiae just prior to death was often not noted on the record unless autopsy was performed and their presence noted. I feel certain that clubbing of the fingers is found in more patients than the 37.4 per cent recorded in this series. Certainly among those patients seen and repeatedly examined by me, this feature was found in at least 50 per cent.

The finding that many of the patients in whom the disease was recognized and treated early had normal urine as shown by repeated analyses was rather striking and surprising.

That transient bacteremia follows dental extractions has been amply proved and emphasized in the literature. An apparently direct relationship to exodontia was found in 13.3 per cent of this series. The connection between abortion or postpartum infection and the onset of

bacterial endocarditis is more difficult to establish. In 2 patients there could be no question about the causal relationship, and in 8.2 per cent of the patients there seemed to be a direct connection between inflammatory disease of the pelvic region and bacterial endocarditis.

Three patients in this series had auricular fibrillation at the time of admission to the hospital. With regard to one of them it could be definitely established that this was present for two years prior to the development of the bacterial endocarditis. In another the auricular fibrillation probably developed after the bacterial endocarditis. The duration of auricular fibrillation in the third patient was unknown, although he had had rheumatic heart disease for twenty-two years.

The onset of the symptoms of endocarditis began with acute embolization, without a previous recent illness, in 11 patients, or 6.7 per cent. Many of these were initially admitted to the neurologic or the neurosurgical service.

In 1 patient fever was absent during the period of hospitalization. This, however, was undoubtedly a terminal manifestation. In 1 patient no cardiac murmur was ever heard. This patient also had repeatedly negative blood cultures. Autopsy revealed bacterial involvement of the pulmonary valve.

Definite evidence of pulmonary embolism was found in 17 of 24 patients with congenital heart disease believed to have communication between the greater and lesser circulatory systems.

White [2] stated that in cases of subacute bacterial endocarditis a leukocyte count of 12,000 to 16,000 is common but that the white blood cell count is "at times recorded even at a normal figure." Christian [3] stated that leukocytosis "is the rule; usually moderate, it may be marked." Kinsella [4] stated that "the white cell count is often between 12,000 and 18,000, although normal counts are not uncommon." Gow [5] wrote that the septicemic state is in general associated with leukocytosis and that in cases of subacute bacterial endocarditis a count varying between 10,000 and 20,000 per cubic millimeter is the rule, but that leukopenia occurs fairly frequently. In our series, it will be noted, 53.4 per cent of the patients had a white blood cell count between 5,001 and 10,000 per cubic millimeter. This has been of importance in teaching students inasmuch as it has been a common observation that students tend to disregard the likelihood of bacterial endocarditis if repeated white

2. White, P. D.: Heart Disease, ed. 3, New York, The Macmillan Company, 1944.

3. Osler, W.: Principles and Practice of Medicine, edited by H. A. Christian, ed. 15, New York, D. Appleton-Century Company, Inc., 1944.

4. Kinsella, R. A., in Cecil, R. L.: Textbook of Medicine, ed. 6, Philadelphia, W. B. Saunders Company, 1943.

5. Gow, A. E.: Discussion on the Clinical Significance and Course of Subacute Bacterial Endocarditis, Brit. M. J. **2**:307 (Aug. 28) 1920.

blood cell counts are normal. Only 13.1 per cent of the patients had a leukocyte count of over 15,000 per cubic millimeter.

A review of the records of the University Hospital revealed that the hemoglobin content was frequently reported in percentage only, without indication of the standard being used. Consequently, it was necessary to use the total red blood cell count as an index of anemia. Although the color index is frequently less than 1, the total red cell count is probably as reliable an index of the anemia characteristic of this disease as is the hemoglobin value. In 70 per cent of the cases the red blood cell count was below 4,000,000 per cubic millimeter.

RELATION OF DISEASE TO AGE AND SEX

Libman and Friedberg [1] reported that two thirds of their patients were in the third and fourth decades of life. The oldest patient seen by them was 74, and the youngest was 4. The distribution in the present series closely parallels that cited by White.[2] It was found to be: 2.4 per cent from 1 to 10 years, 19.4 per cent from 11 to 20, 36.4 per cent from 21 to 30, 19.4 per cent from 31 to 40, 12.1 per cent from 41 to 50, 6.7 per cent from 51 to 60, 4 per cent from 61 to 70 and 1.2 per cent over 70. In this series 55.8 per cent of the patients were found to be in the third and fourth decades. The youngest patient seen was a 4 year old girl with involvement of the tricuspid valve; no underlying valvular disease was established at autopsy. The oldest patient was a man of 72 with subacute bacterial endocarditis superimposed on a sclerotic aortic valve. One man of 71 had involvement of the mitral and tricuspid valves superimposed on old rheumatic valvulitis.

Blumer [6] found that 60 per cent of 328 patients were males. In this series the distribution was 55.8 per cent males and 44.2 per cent females.

UNDERLYING HEART DISEASE

Christian [8] stated that a study of 150 adults with subacute bacterial endocarditis showed rheumatic heart disease to be the underlying condition in 90 per cent. White [2] wrote that rheumatic heart disease was the predisposing factor in about 80 per cent and congenital heart disease in about 5 per cent. In the present series the percentage distribution found, on the basis of clinical diagnoses, was: rheumatic heart disease, 66.1; congenital heart disease, 15.2; both rheumatic and congenital heart disease, 1.2 (2 patients); arteriosclerotic heart disease, 0.6; syphilitic heart disease, 1.8; myocardial infarction, 0.6; unknown underlying disease or none, 13.9. In comparsion, the percentages when only patients examined post mortem (58) were considered were:

6. Blumer, G.: Subacute Bacterial Endocarditis, Medicine **2**:105 (May) 1923.

rheumatic heart disease, 60.3; congenital heart disease, 13.8; both congenital and rheumatic heart disease, 3.4; arteriosclerotic heart disease, 1.7; syphilitic heart disease, 3.4; unknown underlying disease or none, 17.2. One of the patients listed as having congenital heart disease had an interauricular septal defect, and although all the valves were involved in the bacterial endocarditis, the margins of the septal defect were normal; there was no evidence of other underlying heart disease. It is not believed that the high percentage listed under "unknown or none" represents bacterial endocarditis superimposed on previously normal valves. It is possible that in rare instances subacute bacterial endocarditis may have developed in previously normal valves, but in the majority of this group preexisting heart disease was present but not classifiable on the basis of the observations made at autopsy. The listing of 1 patient as having myocardial infarction as the predisposing factor is based on clinical information only. It was known that a precordial systolic murmur appeared, following a posterior infarction, seven years prior to the patient's bacterial endocarditis. No other murmur was ever heard.

PATHOLOGIC AND BACTERIOLOGIC ASPECTS

The distribution of the bacteria observed in blood cultures in 157 of the 165 cases of subacute bacterial endocarditis is given in table 2. In 8 of the 165 cases no blood cultures were made during life, and the diagnosis was made only at autopsy. In 7 instances the antemortem

TABLE 2.—*Results of Culture of Blood in One Hundred and Fifty-Seven Cases of Subacute Bacterial Endocarditis* *

Streptococcus Viridans (Alpha)	Streptococcus Hemolyticus (Beta)	Streptococcus Anhemolyticus (Gamma)	Gram-positive Cocci in Chains	Gaffkya Tetragena (Micrococcus Tetragenus)	Gram-negative Pleomorphic Rods	Staphylococcus Albus	Staphylococcus Aureus	Brucella Abortus	Clostridium	Negative but Positive at Autopsy
126	3	12	3	1	1	1	1	1	1	7
80.2%	1.9%	7.6%	1.9%	0.6%	0.6%	0.6%	0.6%	0.6%	0.6%	4.5%

* In 8 of the 165 cases blood cultures were not made, the diagnosis being made at autopsy only.

blood cultures were negative, but positive cultures were obtained from the heart's blood at autopsy. Since postmortem blood cultures are notoriously unreliable, as a terminal bacteremia with mixed organisms is not uncommon, these cases have not been included in the tabulation. In 4 of them hemolytic streptococci and in 1 gamma streptococci were isolated. It is entirely possible that the instance in which gram-negative pleomorphic rods were isolated represented an infection with the Pfeiffer bacillus.

Whether or not the hemolytic streptococci in 4 of the 7 postmortem blood cultures represented the actual causative agent cannot be definitely stated. The 3 instances in which hemolytic streptococci were isolated ante mortem are included because the clinical course and features in each were those of subacute bacterial endocarditis. The 1 case of endocarditis due to Staphylococcus aureus is presented under the heading "Results with Penicillin." As stated under that heading, the clinical appearance was that of the subacute form of bacterial endocarditis.

The Clostridium isolated was from a patient treated with penicillin. This patient presented the typical picture of subacute bacterial endocarditis superimposed on rheumatic heart disease, but the blood cultures were persistently negative during life. The terminal symptoms were suggestive of acute myocardial infarction. At autopsy, the aortic cusps had vegetations, and there were purulent mycotic aneurysms of the coronary arteries. The Clostridium was isolated both from the center of the partially fixed (solution of formaldehyde U. S. P.) aortic vegetations and from the mycotic aneurysms. Its position within the genus was not determined.

One patient showing endocarditis due to Cryptococcus histolyticus is included neither in the table of blood cultures nor in the series selected for this study, because the endocardial involvement was merely an incidental finding at autopsy in a case of general cryptococcosis.

When studies of strains were done (since 1942), the streptococci of the viridans group were found to be almost always of the salivarius strain. In connection with the studies of strains, susceptibility was determined in vitro in most instances after 1942. Occasionally organisms were encountered which could not be grown in proper mediums and under conditions suitable for in vitro studies of susceptibility. In those cases in which oxophenarsine hydrochloride, neoarsphenamine, acriflavine and congo red were included in the study of inhibition of bacterial growth, inhibition was never produced by concentrations obtainable in vivo. Of the sulfonamide compounds, sulfathiazole generally gave complete inhibition in greater dilution than any others. In a considerable number of cases, however, the level of inhibition was the same for both sulfathiazole and sulfadiazine. For 2 patients who were under treatment with sulfathiazole, studies of susceptibility were repeated two to three weeks after the initiation of therapy. Comparison of the inhibitory levels showed that the organisms had acquired in vitro resistance to the sulfonamide compound being used in therapy but not to other sulfonamide compounds. This is discussed later.

In the cases of bacterial endocarditis in which autopsy was performed (58) major involvement was found as follows: mitral valve, 21; aortic valve, 10; mitral and aortic valves, 14; interventricular septal

defect and aortic valve, 1; mitral and tricuspid valves and interventricular septal defect, 1; tricuspid and pulmonary valves and interventricular septal defect, 1; pulmonary valve and pulmonary artery, 1; tricuspid valve, 2; aortic valve and ductus arteriosus, 1; aortic and tricuspid valves, 1; aortic and pulmonary valves, 1; mitral and tricuspid valves, 2; mitral, tricuspid, pulmonary and aortic valves, 1; pulmonary, tricuspid and mitral valves, 1.

Recent or old myocardial infarcts or both were found in 25 per cent of the cases in which autopsy was performed. White [2] stated that cardiac infarction is "very rare." In only a few cases was myocardial infarction suspected before death. In 2 cases in which autopsy was not performed there was electrocardiographic evidence of posterior myocardial infarction; one of the patients had suffered his infarction seven years prior to the development of bacterial endocarditis, and one had had anginal pain for six years, although the time of infarction was not known. This would suggest that even in patients successfully treated for bacterial endocarditis, if the disease has been well established, some loss of cardiac reserve may occur beyond that anticipated from the valvular damage. With the known frequency of embolic necroses and small pyemic abscesses in the myocardium at autopsy in cases of subacute bacterial endocarditis, it is not surprising that myocardial infarcts were found so frequently.

RESULTS OF TREATMENT PRIOR TO THE ADVENT OF SULFONAMIDE COMPOUNDS

Prior to the use of sulfonamide compounds, there were 69 patients who either received no treatment aimed at eradicating the infection or were given treatment in general use prior to the advent of sulfonamide therapy. Data on these patients are summarized in table 3.

Many of them received sodium cacodylate. Some received autogenous vaccines. A few were given metaphen intravenously. More than half received one or more blood transfusions. All except 3 are known to have died from subacute bacterial endocarditis. The 3 on whom no follow-up record was obtainable were severely ill at the time of discharge. Two of the 3 were discharged for terminal care at home. These 2 undoubtedly died of the disease, and there is nothing on the record of the third that would suggest recovery as likely.

In a series of 2,596 cases collected from the literature, Lichtman [7] found the incidence of spontaneous recovery to be 1 per cent. In the present series, there was no recovery in the 66 patients in this group on whom follow-up reports were obtained.

7. Lichtman, S. S.: Treatment of Subacute Bacterial Endocarditis, Ann. Int. Med. **19**:787 (Nov.) 1943.

RESULTS WITH SULFONAMIDE COMPOUNDS ALONE

Fifty-three patients were included in this group. There were 2 patients on whom follow-up reports were not obtained. Of the 51 patients whose status was determined, all but 1 were dead. Lichtman [7] arbitrarily defined adequate treatment for this group as a minimum of two weeks of intensive sulfonamide therapy. Thirty-nine patients were so treated. My patients are included in table 3.

TABLE 3.—*Results of Various Forms of Treatment of Subacute Bacterial Endocarditis*

	Present Series					Lichtmen, 1943 [7]		Total Percentage of Recoveries, Both Series
Treatment	Patients	Number Known to Be Dead	Number Known to Be Alive	Number on Whom There Is No Follow-Up Report	Adequacy of Treatment	Patients	Number Who Recovered	
Such drugs and forms of therapy as were in use prior to advent of sulfonamide compounds	69	66	0	3	.....	2,596	25 (0.96%)	0.94
Sulfonamide compounds only	53*	50	1† (2%)	2	39 had sulfonamide compounds for 2 weeks or more	480	21 (4.3%)	4.2 ‡
Sulfonamide compounds and heparin	5	5	0	..	3 received both for at least 2 weeks	109	7 (6.4%)	6.2 ‡
Sulfonamide compounds and hyperthermia produced with typhoid bacillus vaccine	16	14	2 (12.5%)	..	7 adequately treated by the standards set forth in text; 28.5% of these recovered	45	7 (15.5%)	
Sulfonamide compounds, neoarsphenamine and hyperthermia produced with typhoid bacillus vaccine	8	8	0	..	6 adequately treated by the standards set forth in text; none recovered			15.5 (of 58 patients)
Arsenicals alone	2	2	..	..	See text			

* One patient had successful ligation of patent ductus arteriosus without benefit.
† Patient was D. H. (see report of case).
‡ Percentage includes only adequately treated patients from the present series (see text).

The living patient, D. H., is of some interest. He was admitted to the hospital in January 1942, after a grippal type of onset of subacute bacterial endocarditis in November 1941. His condition was diagnosed as an interventricular septal defect with repeated pulmonary infarcts and pleural effusion. The spleen was questionably palpable. Three blood cultures, made at weekly intervals, were positive for Streptococcus viridans, although the patient was receiving sulfadiazine. He received sulfadiazine for twenty-three days, with defervescence, although slight elevations of temperature persisted most of the time. Resolution of some of the pulmonary infarcts was complete, and the more recent ones were resolving at the time of the patient's discharge in February 1942. He was seen in the clinic three weeks later, feeling well but having noted fever on several occasions.

By April 1942 he was feeling well and gaining weight. A roentgenogram in July 1943 revealed no abnormality. A preemployment roentgenogram in October 1943 revealed tuberculosis at the apex of the right lung. He was readmitted to the University Hospital in July 1944 for thoracoplasty. No evidence of subacute bacterial endocarditis was noted while he was in a nearby sanatorium for patients with tuberculosis or during this period in the University Hospital. The cardiac status was otherwise unchanged.

It cannot be definitely stated that his recovery was not spontaneous, but it was probably due to the treatment with sulfadiazine.

A second patient, W. P., was previously observed by Field, Hoobler and Avery [8] and included as recovered in the report of Lichtman.[7] This patient was treated with sulfapyridine in November and December of 1939. He was considered as cured and was as well as ever in April 1941. He died in 1943, and autopsy was performed. Death was apparently due to congestive heart failure. There was evidence of old splenic infarcts and of old and recent renal infarcts. The heart confirmed the clinical diagnosis of the tetralogy of Fallot. An aortic cusp was thickened and slightly granular. Microscopic examination of this cusp showed chronic productive valvulitis with areas of necrosis in the interior of the valve. There were several small foci of greater activity involving the endothelium and the subendothelial supporting tissue. No vegetations were present, but the pathologist felt that active valvulitis was still present. No organisms were demonstrated by Gram's method.

Although this patient did not exhibit the clinical features generally associated with the bacteria-free stage of subacute bacterial endocarditis and although death from congestive heart failure and pneumonia at 27 in a person with the tetralogy of Fallot is certainly not unusual, the results of autopsy suggest that this represents a bacteria-free stage of the disease.

In Lichtman's report [7] there is mention of a 4 per cent incidence of recovery in 489 patients treated by sulfonamide compounds alone (one of whom was W. P., discussed previously). In the 51 patients whose entire course was known in the present series, recovery resulted in approximately 2 per cent (1 patient). However, an additional patient (W. P.) was clinically well for three years.

RESULTS WITH COMBINED SULFONAMIDE-HEPARIN THERAPY

In 1939 the preliminary report of Kelson [9] on the use of heparin and sulfapyridine increased the hope that bacterial endocarditis might become more amenable to sulfonamide therapy. The later report of Leach and associates [10] was not as encouraging. Lichtman's review [7]

8. Field, H., Jr; Hoobler, S. W., and Avery, N. L., Jr.: Results of Chemotherapy in Subacute Bacterial Endocarditis, Am. J. M. Sc. **202**:798 (Dec.) 1941.

9. Kelson, S. R.: A New Method of Treatment of Subacute Bacterial Endocarditis Using Sulfapyridine and Heparin in Combination, J. A. M. A. **113**:1700 (Nov. 4) 1939.

(Footnotes continued on next page)

of 1943 includes a total of 109 patients treated with heparin and sulfonamide compounds, with an incidence of recovery of 6.5 per cent. Lichtman arbitrarily defined adequate treatment as at least two weeks of intensive sulfonamide medication together with two weeks of heparinization with a blood coagulation time of one hour.

The present series includes only 5 patients treated according to the method (table 3), all of whom died. The group is extremely small because of general dissatisfaction with the method at the University Hospital.

RESULTS WITH COMBINED SULFONAMIDE-FEVER THERAPY

White and Parker [11] reported in 1938 that the effect of sulfanilamide on beta hemolytic streptococci in vitro was enhanced by elevated temperatures. This was followed by a further report by White [12] in 1939 on the relationship between temperature and the streptococcidal activity of sulfanilamide and sulfapyridine in vitro. It was shown that under the stated conditions beta hemolytic streptococci are much more susceptible to sulfanilamide and sulfapyridine at from 39 to 40 C. than they are at 37 C.

Sherman [13] had previously shown that some strains of Streptococcus salivarius are not as resistant to heat as other viridans streptococci.

Lichtman's report of 1943 [7] includes 61 patients treated with artificial hyperthermia and sulfonamide compounds, with a recovery rate of 6.5 per cent. In the same report he mentioned 45 patients treated with combined chemotherapy and hyperpyrexia produced by intravenous administration of bacterial vaccine made from the typhoid bacillus, U.S.P., with an incidence of recovery of 15.5 per cent.

There were 16 patients in the present series who were treated by chemotherapy and pyretotherapy combined. Fever was produced by intravenous administration of bacterial vaccine made from the typhoid bacillus, U. S. P. Before the use of the continuous intravenous drip of the vaccine in isotonic solution of sodium chloride, milk was given intramuscularly about four hours before the administration of the vaccine in an attempt to prolong the peak temperature without multiple injections of the vaccine. A definite program of management for these

10. Leach, C. E.; Faulkner, J. M.; Duncan, C. N.; McGinn, S.; Porter, R. R., and White, P. D.: Chemotherapy and Heparin in Subacute Bacterial Endocarditis, J. A. M. A. **117**:1345 (Oct. 18) 1941.

11. White, H. J., and Parker, J. M.: The Bactericidal Effect of Sulfanilamide upon Beta Hemolytic Streptococci in Vitro, J. Bact. **36**:481 (Nov.) 1938.

12. White, H. J.: The Relationship Between Temperature and the Streptococcidal Activity of Sulfanilamide and Sulfapyridine in Vitro, J. Bact. **38**:549 (Nov.) 1939.

13. Sherman, J. M.: The Streptococci, Bact. Rev. **1**:3 (Dec.) 1937.

patients was developed, with the result that there was a gratifying degree of tolerance for the periods of hyperpyrexia. It was found that the rigor can be largely suppressed, the cyanosis prevented, the pulse rate lowered and the discomfort decreased by administration of 100 per cent oxygen by the Boothby mask. This has no effect on the febrile response. The administration of oxygen was started about fifteen minutes before the anticipated time of the rigor. It was discontinued before the appearance of diaphoresis. Data on these patients are summarized in table 3.

At the time these patients were being treated, some of the house physicians felt that the method was not receiving a fair trial inasmuch as no selection of patients was practiced. However, since it was felt that the method was the best that could be offered, all patients who were able to tolerate a single session of hyperthermia were so treated. Despite the obviously hopeless condition of some, it was remarkable how well the treatment was tolerated by most of the patients. One patient died, apparently of exhaustion, on the day following his twelfth paroxysm of fever, which was unusually prolonged and severe.

In an attempt to evaluate the results better, the group has been divided into patients adequately and patients inadequately treated. Adequate treatment has been arbitrarily defined as a minimum of thirty-two hours of fever with the temperature at or above 103 F., produced by at least nine paroxysms, with maintenance of the generally accepted therapeutic blood levels of the sulfonamide compounds used—5 to 10 mg. per hundred cubic centimeters for sulfathiazole and 10 mg. per hundred cubic centimeters for sulfadiazine. Some of the patients who might have tolerated adequate treatment as so defined did not receive it for various reasons. The maximum number of hours of induced fever with the temperature at or above 103 F. was fifty, given by thirteen inductions.

Both of the patients who recovered had rheumatic heart disease. One, whose bacterial endocarditis was of about two months' duration, was treated in 1941. He was in excellent health after this therapy and was followed until January 1945. The second patient, whose disease was of four months' duration, was treated in 1942. She was followed until January 1945 and remained entirely well. After their initial discharge, both were subsequently readmitted on two occasions for exodontia with prophylactic chemotherapy.

RESULTS WITH COMBINED SULFONAMIDE-NEOARSPHENAMINE-FEVER THERAPY

In May 1942, Osgood [14] reported on the use of neoarsphenamine in the treatment of subacute bacterial endocarditis and severe systemic

14. Osgood, E. E.: Neoarsphenamine Therapy of Bacterial Infections, Arch. Int. Med. **69**:746 (May) 1942.

staphylococcic infections. In his article he suggested combining hyperthermia with neoarsphenamine, and with sulfonamide compounds as well, if the organism showed susceptibility to both sulfonamide compounds and neoarsphenamine in bone marrow cultures. He reported promising results.

Table 3 summarizes the results obtained when neoarsphenamine, sulfonamide compounds and bacterial vaccine made from the typhoid bacillus, U. S. P., were used in conjunction. Here, too, the group was divided into patients who received adequate and those who received inadequate treatment. Adequate treatment was arbitrarily defined as including a minimum of thirty-two hours of fever with the temperature at or above 103 F., induced by at least nine paroxysms, maintenance of the generally accepted therapeutic blood levels of the sulfonamide compounds and administration of at least one course of neoarsphenamine as outlined by Osgood for the treatment of bacterial endocarditis, namely, 0.8 mg. of neoarsphenamine per pound of body weight every four hours for four doses on the first day and then every eight hours for a total of six days.

None of these patients recovered. Complications due to the treatment with neoarsphenamine occurred in 3 of the 8 patients.

In addition to the 8 patients reported on in table 3, 2 patients received arsenicals alone. The one received adequate neoarsphenamine therapy as recommended by Osgood, and the other received 1,200 mg. of oxophenarsine hydrochloride during five days for syphilis. The latter patient refused treatment for his bacterial endocarditis. Both patients died of their disease. Data on them have been included, under a separate heading, in table 3.

If an attempt is made to evaluate the effectiveness of the combined sulfonamide-fever therapy, the patients adequately treated with this therapy may be combined, as indicated in table 3, with those patients receiving adequate sulfonamide-neoarsphenamine-fever therapy. This can be done inasmuch as neoarsphenamine had no beneficial effect. It cannot be stated that it may not have had a deleterious effect on the sulfonamide-fever therapy, but there is no published evidence to suggest this. By combining the two adequately treated groups, one finds that 2 of the 13 patients recovered (15.4 per cent). This is, of course, too small a group to have any statistical significance, but the figure is in striking agreement with Lichtman's 15.5 per cent recovery of 45 patients.

RESULTS WITH PENICILLIN

Because of the rigid control of penicillin and the high military priority, amounts adequate for clinical use in the treatment of subacute bacterial endocarditis were not soon available. Early reports, known to all,

were indeed discouraging. However, with the report of Loewe, Rosenblatt, Greene and Russell [15] in January 1944, interest in penicillin therapy of bacterial endocarditis was revived. In addition, the supply of penicillin for civilian use was then increased.

Table 4 summarizes the results obtained at the University Hospital with the use of penicillin. Of the 12 patients who received this antibiotic agent, 7 experienced an apparently successful result.

Even in this small group of patients it became apparent that the continuous intravenous drip method of administration was not satisfactory. This method was attempted in 6 cases, and in only 2 was it tolerated for fourteen days. Thrombophlebitis occurred in every patient receiving penicillin solutions by continuous intravenous drip.

At this hospital experience with mixtures of yellow wax, peanut oil and penicillin was disappointing. Considerable difficulty was found in getting uniform preparations, and at times the penicillin was found to have separated from the emulsion. In addition, the nurses complained about the difficulty of drawing the emulsion from the vial and administering it through any gage of needle less than no. 18. It was felt also that the introduction of oil-wax-penicillin mixtures was not without danger of future complications in the form either of "paraffinomas" or of sensitization phenomena.

Intermittent intramuscular or subcutaneous administration of penicillin was satisfactory except for the obvious discomfort caused the patient and the interference with rest.

Early in 1945 the continuous intramuscular drip method was employed. In practice this was sometimes a deep subcutaneous infusion. The desired daily dose of penicillin was diluted in 750 to 1,000 cc. of isotonic solution of sodium chloride or 5 per cent dextrose solution and injected into the thigh through a 21 gage needle. A pillow placed lateral to the selected thigh left the patient free to move normally in bed, and there was no interference with sleep. Regulation of the speed of hypodermoclysis was simple. If about twenty or more hours were utilized for administration, there was little discomfort from distention of the tissue, and nursing care, such as bathing and back rubs, could be given during the hours when penicillin was not being administered. No complications were encountered.

The smallest total dose of penicillin resulting in apparent cure was 2,540,000 units. The largest total dose administered was 21,640,000 units. The patient who received the latter dose had been ill for over a year and experienced occasional embolic episodes. Later, the emboli

15. Loewe, L.; Rosenblatt, P.; Greene, H. J., and Russell, M.: Combined Penicillin and Heparin Therapy of Subacute Bacterial Endocarditis, J. A. M. A. **124**:144 (Jan. 15) 1944.

TABLE 4.—*Data on Patients with Subacute Bacterial Endocarditis Treated with Penicillin*

Patient	Preexisting Lesion of Heart	Probable Date of Onset of Subacute Bacterial Endocarditis and Duration Prior to Administration of Drug	Previous Treatment	Organism in Blood Culture	Susceptibility Expressed as Concentration of Drug Required to Produce Complete Inhibition	Treatment *	Outcome †
J. H., discharged 7/27/44	Rheumatic heart disease, mitral stenosis, mitral insufficiency	? Jan. 1944 (5 mo.)	?	Str. salivarius 1/3/45 neg. 5/23/45 neg.	0.0001 units per cc.	2.8 M penicillin cont. IV for 14 days; 1.395 M penicillin IM for 9 days; total, 4.195 M	Cured; patient entirely well, 1/10/46
H. S., discharged 9/2/44	Congenital heart disease, patent ductus arteriosus	? Jan. 1944 (7 mo.)	?	Str. salivarius	?	1.2 M penicillin cont. IV for 7 days; 2.845 M penicillin IM for 19 days; total, 4.045 M; sulfadiazine for 44 days	Apparently cured; nephritis continues; well, June 1945
C. K., discharged 4/29/44	Congenital heart disease, ? septal defect	? Summer of 1942 (20 mo.)	None	Str. salivarius 11/1/44 neg.	?	2.9 M penicillin cont. IV for 14 days; sulfadiazine for 2 days	Apparently cured
F. G., discharged 10/30/44	Rheumatic heart disease, aortic insufficiency, mitral stenosis, mitral insufficiency, auricular fibrillation	? June 1944 (2 mo.)	Sulfadiazine	Str. salivarius 3/31/45 neg.	0.01 unit per cc.	8.01 M penicillin IM for 52 days; typhoid vaccine IV, four times	Arrested
M. F., died 12/2/44	Rheumatic heart disease, mitral insufficiency	Jan. 1944 (11 mo.)	Sulfonamide compounds	Str. salivarius	0.1 unit per cc.; none with sulfadiazine	1.33 M penicillin IM for 11 days	Death (cerebral embolus)
G. B., discharged 1/12/45	Rheumatic heart disease, mitral stenosis, mitral insufficiency	? Jan. 1944 (11 mo.)	Sulfonamide compounds, 1,380,000 units of penicillin	Str. salivarius, nonhemolytic streptococci	0.1 unit per cc.; none with sulfathiazole or sulfadiazine	7.902 M penicillin IM for 50 days	Death, ? nephritic

N. S., died 7/27/44	Rheumatic heart disease, aortic stenosis, aortic insufficiency, mitral stenosis, mitral insufficiency	? July 1943 (19 mo.)	Sulfadiazine, 2 days	None	?	Cont. IV penicillin 200,000 units per 24 hr. for 5 days; 15,000 units IM every 2 hr. for 6 days; total, 1.78 M in 11 days	Death, subacute bacterial endocarditis at autopsy
E. B., discharged 8/6/44	Congenital heart disease, patent ductus arteriosus	? Jan. 1943 (10 mo.)	?	Str. salivarius 1/9/45 neg. 5/23/45 neg.	0.1 unit per cc.	Ligation of patent ductus arteriosus, 11/2/43; sulfonamide compounds and fever; sulfonamide compounds, neoarsphenamine and fever; cont. IV penicillin, 2.8 M for 13 days; 10.0 M IM for 60 days; total, 12.8 M penicillin in 73 days; typhoid bacillus vaccine fever, 3 days	Cured; patient entirely well, 1/3/46
D. W., discharged 5/27/44	Congenital heart disease, ? tetralogy of Fallot	March 1944 (6 wk.)	Sulfonamide compounds	Str. salivarius	0.0001 unit per cc.	Cont. IV penicillin for 8 days; penicillin IM for 7 days; total, 2.54 M in 15 days	Apparently cured; patient entirely well, April 1945
V. G., discharged 5/1/45	Rheumatic heart disease, aortic stenosis, aortic insufficiency, mitral stenosis, mitral insufficiency	? Jan. 1944 (12 mo.)	1,500,000 units penicillin, May 1944; 1,200,000 units, June 1944; 1,200,000 units, July 1944; 1,100,000 units, plus heparin, Sept. 1944	Str. viridans	0.1 unit per cc.; none with sulfathiazole or sulfadiazine	Total, 21.64 M penicillin in 106 days	Death, 3 mo. after discharge, presumably due to cerebral embolus
T. M., died 3/15/45	Rheumatic heart disease, mitral stenosis, mitral insufficiency	July 1944 (8 mo.)	None	Str. salivarius	?	Cont. subcutaneous penicillin for 9 days; total, 3.08 M; sulfamerazine 3 Gm. a day for 8 days	Death (cerebral embolus)
J. M., discharged 5/20/45	Rheumatic heart disease, mitral stenosis, mitral insufficiency	Jan. 27, 1945 (5 wk.)	None	Staph. aureus	?	Sulfathiazole for 14 days; cont. subcut. penicillin for 31 days; intermittent IM penicillin 7 days; total, 11.56 M in 38 days	Arrested; patient well and working, Sept. 1945

* M stands for million units; cont. IV, for continuous intravenous drip; IM, for intramuscular injections.

† If the patient presented no symptoms at three months, the disease was considered ? arrested; from three to six months, arrested; from six to twelve months, apparently cured, and from twelve months on, cured.

apparently became sterile. Prior to discharge she suffered several small embolizations without apparent sequelae.

The percentage of initially good results obtained in this group of 12 patients is 58.3. In reports of 98 cases collected from the literature 70.4 per cent of patients are said to have recovered. By combining the two groups, one obtains a recovery rate of 69 per cent for 110 patients. These figures do not include patients reported on during the period of inadequate supply of penicillin.

Two of the patients in the penicillin-treated group are of unusual interest.

One patient, E. B., was admitted to the hospital, Oct. 13, 1943, with a patent ductus arteriosus and a history of fever since January 1943. During this ten month period she had had her antrums needled in February, an abscessed tooth extracted in March and a Caldwell-Luc operation on the left antrum in July. Blood cultures made at another hospital in September were "positive." The ductus arteriosus was ligated at the University Hospital three weeks after the patient's admission. Blood cultures made before and after the operation were positive for Str. salivarius. Despite treatment with sulfonamide compounds and combined therapy with neoarsphenamine, sulfonamide compounds and fever, the blood cultures remained positive although the patient seemed to maintain a fairly good clinical condition. After several unsuccessful attempts to secure penicillin, 2,800,000 units was obtained for continuous intravenous administration. This was started on approximately the four hundredth and eighty-third day of her illness. Severe thrombophlebitis of the veins of the arms developed on the sixth day of administration. Pneumonia developed, and Pseudomonas schuylkilliensis was isolated from the blood and the sputum and also from the penicillin solution in the infusion flask (not from the ampule of penicillin). The course was completed by the intramuscular route. Blood cultures became negative for Str. salivarius. Treatment was concluded on May 12, 1944. During the patient's attack of pneumonia, a caseous mediastinal lymph node evidently broke down, and the sputum became positive for Mycobacterium tuberculosis by concentrate, culture and guinea pig inoculation. Blood cultures again became positive for Str. salivarius, and the intramuscular administration of penicillin (180,000 units a day) was started again on June 6 and continued until August 6. Since then blood cultures have remained sterile. Clinical recovery was prompt and striking. Full activity was gradually undertaken by the patient, without cardiac symptoms or any further evidence of tuberculosis. She was in excellent general condition and without evidence of infection on Jan. 3, 1946.

The second patient of unusual interest was a 21 year old university student who was working as a technician in the medical outpatient laboratory. This girl, J. M., had a tooth extracted without chemotherapy on Feb. 27, 1945. Rheumatic mitral stenosis and insufficiency had developed some years before. Symptoms of bacterial endocarditis developed on April 1. The appearance was that of subacute rather than acute bacterial endocarditis, despite the isolation of Staph. aureus (coagulase positive) in blood cultures. Treatment was instituted on April 5. Every day for the first week 500,000 units of penicillin was given by the continuous subcutaneous drip method. Thereafter the dose was reduced to 300,000 units a day until May 5, when the dose was further reduced. Sulfathiazole was also given during the first fourteen days of treatment. Recovery was

prompt after April 20. The patient completed the academic term, served as a counselor in a summer camp and is now working as a laboratory technician.

COMMENT

In order to approach the therapy of any disease rationally, it is necessary to have a thorough understanding of the pathologic changes produced as well as a knowledge of the characteristics of the causative agent.

There is an abundance of literature on the pathologic aspects of bacterial endocarditis, both natural and experimental. I have found that the articles of Nedzel [16] and Allen [17] are most helpful in giving a basic understanding of the process involved. Libman and Friedberg [1] in their monograph have discussed the pathologic aspects of the naturally occurring disease at some length.

Allen [17] described the vegetations in bacterial endocarditis as consisting of three zones: a proximal layer of fibrin, platelets, red blood cells, white blood cells and necrotic and necrobiotic shreds of valvular elastic and collagenous connective tissue; a middle zone made up largely of bacteria, and an outermost layer of fibrin in which red blood cells and a sprinkling of white blood cells are enmeshed. The major portion of the vegetation underlies the bacteria. Growth of the vegetation may occur both by destructive, ulcerative activity at the base and by deposition of blood elements superficially. Allen commented that the severe necrosis and edema, with separation of the elastic and collagenous fibers, are highly suggestive of a response to an altered local reactivity of tissue. Nedzel's [16] description of the events occurring after the intravenous injection of pitressin similarly suggests altered local reactivity of tissue.

When the diagnosis of bacterial endocarditis can be made early, before the vegetations are large, the lesions may be attacked at both the base and the free surface. In such instances an effective antibacterial agent which does not interfere with the natural body defenses may initiate healing, with a minimum of valvular deformity resulting. It is in this type of lesion that heparin might serve as a worth while adjuvant. By inhibiting further thrombotic activity in zones 1 and 3, heparin might allow healing to occur with less distortion of the valve and a smaller scar.

After the disease is well established and the vegetations are of significant size, the indications for heparin are less apparent. In itself the drug is not antibacterial. It does not dissolve fibrin. It probably does not "loosen" already formed thrombotic material, since embolization itself does not seem to be more frequent with the use of heparin than without it. The healing of such vegetative lesions probably takes

16. Nedzel, A. J.: Experimental Endocarditis, Arch. Path. **24**:143 (Aug.) 1937.

17. Allen, A. C.: Nature of Vegetations of Bacterial Endocarditis, Arch. Path. **27**:661 (April) 1939.

place by fibroblastic proliferation, macrophagocytic activity, leukocytic phagocytosis and endothelial proliferation. Fibrosis may later be followed by calcification. If sterilization of the blood stream can be effected, the deposition of sterile fibrin over the surface of the vegetation may be desirable. Healing may take place, with the invading bacteria being destroyed or, as in tuberculosis, being enclosed in a relatively avascular scar. Such fibrotic lesions might harbor viable organisms for some time, which are prevented from further activity only by their own low virulence and the wall of fibrous connective tissue about them.

If sufficient bacteriostasis is to occur to affect greatly the basilar ulcerative process, it probably must take place by way of the capillaries which have been formed in the affected area rather than by penetration of the thrombus and cellular debris and of the free surface of the vegetation. Hence, it is logical to seek as adjuvants to the antibacterial drug agents which will stimulate the immune forces of the body, promote invasion of the tissue by the leukocytic elements of the blood, accelerate or initiate the activity of fixed tissue macrophages, fibroblasts and angioblasts and increase endothelial proliferation. Such agents will, in short, hasten and stimulate the reparative processes of the body as a whole and of the tissues involved locally. Foreign protein therapy (e. g. the administration of bacterial vaccine made from the typhoid bacillus, U. S. P.) is alleged to have such effects.

Under normal circumstances man is able to clear a large number of bacteria from the blood stream without incident. When bacteria have lodged in tissues with poor local defense and initiated cellular necrosis, they are in part protected by the products of cellular death. Anything which will increase the local defense of the tissues may be helpful. Foreign protein therapy is said to produce a partition of the polymorphonuclear leukocytes, sending more of them out of the blood stream and into the tissues. The activity of the histiocytes is enhanced; they tend to proliferate and migrate to form a subendothelial "polster." Fibroblastic and endothelial cell proliferation may be speeded up. The antibody levels in the blood of patients with subacute bacterial endocarditis are generally good, and little is expected from immunotransfusion in this respect. In those cases in which the opsonocytophagic index was determined for the patient's own organisms, this was increased after the intravenous administration of the vaccine made from the typhoid bacillus.

The enhancement of the antibacterial action of sulfonamide compounds by hyperpyrexia, as reported by White and Parker [11] and by White,[12] has been questioned by Hamilton and Hamilton.[18] In working

18. Hamilton, B. W., and Hamilton, T. R.: Pathology and Bacteriology of Streptococcus Endocarditis in Relationship to Sulfonamide Chemotherapy:

(Footnote continued on next page)

with viridans streptococci and enterococci, they concluded that sulfathiazole was no more effective in vitro at 40 C. than at 37 C. In some instances it was less effective at elevated temperatures. When they used the Lancefield group A streptococci, their work was confirmatory of that of White.[12] However, some strains of Str. salivarius are not resistant to heat. Since it is this organism which is most frequently encountered in subacute bacterial endocarditis, hyperpyrexia may be of value in some instances. The work of the Hamiltons indicates the advisability of making studies of susceptibility at both 37 and 40 C. Even though fever therapy may at times have no additive effect on the action of the sulfonamide compounds, the beneficial effects of foreign protein therapy probably justify its use. However, in cases in which hyperpyrexia is not beneficial, foreign protein therapy could be given with the avoidance of high temperatures.

The problem of the development of resistance by the agents of disease to the substances which are used to overcome them is an important one. Acquisition of resistance or tolerance to sulfonamide compounds has been repeatedly demonstrated. As previously noted, 2 of the patients in this series, the only 2 who were tested for it, showed the development of specific resistance to sulfonamide compounds in vitro. In 1 instance it required ten times the original bactericidal level to produce this effect, and in the second the degree of resistance was of the order of one hundred times.

Some of the patients who were treated by combined chemotherapy and pyretotherapy were given intensive treatment initially. This was done in the belief that the organisms might rather rapidly develop resistance to the sulfonamide compounds used unless they were destroyed by the drug or by the body defenses plus the bacteriostatic action of the drug. These patients were given large initial doses of sulfathiazole or sulfadiazine to produce a satisfactory blood level rapidly. Fever therapy was then instituted with daily inductions during the first three days. Oral intake of the sulfonamide compound was supplemented by intravenous administration of 2.5 to 5 Gm. of the sodium salt at the time of injection of the vaccine made from the typhoid bacillus. To several, including 1 of the cured patients, whereas sulfathiazole was given by mouth, sulfadiazine sodium was given intravenously.

If any conclusions can be drawn from in vitro studies of susceptibility, it can be said that the streptococci of the viridans type isolated in clinical cases of subacute bacterial endocarditis in the past eighteen to twenty-four months exhibit a degree of resistance to sulfonamide

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II. The Effect of Temperature Elevation on the Action of Sulfathiazole upon Endocarditis Strains of Streptococcus Viridans, Enterococci and Group A Streptococci, Am. J. Clin. Path. **14**:502 (Oct.) 1944.

compounds rarely seen in the earlier days of sulfonamide therapy. With the last 6 or 7 patients for whom such studies were made, 3 of whom are included in table 4, no inhibition was obtained with a concentration of sulfadiazine or sulfathiazole of 100 mg. per hundred cubic centimeters. This was so unusual that the studies were repeated numerous times, but always with the same result. From conversations with others making similar studies, I learned that this experience is not unique in this hospital's laboratories. It suggests that the widespread use of sulfonamide compounds has brought about the perpetuation of resistant strains of Str. viridans. It is probably fortunate that penicillin appeared when it did. It is doubtful whether the results of treatment of bacterial endocarditis with sulfonamide compounds would have continued at even the modest level achieved.

There has been published recently evidence that staphylococci may acquire resistance to penicillin in vivo.[19] This resistance may be a permanent characteristic. It is entirely likely that evidence of acquired resistance to penicillin in streptococci will be forthcoming. Consequently, it is extremely important that large initial doses of penicillin should be used in any case of infection in which its use is indicated. At the present time the administration of no less than 500,000 units of penicillin a day is advisable for the first two or three weeks of treatment in bacterial endocarditis. If positive blood cultures persist after three days of treatment, this dose might well be increased to 2,000,000 units a day.

SUMMARY AND CONCLUSIONS

One hundred and sixty-five cases of subacute bacterial endocarditis occurring between 1934 and 1945 have been surveyed with regard to the clinical, bacteriologic and pathologic features of the disease and with particular regard to the results of the various methods of treatment used.

In patients with subacute bacterial endocarditis leukocytosis is as frequently absent as it is present.

The pathology of the disease carries implications as to treatment.

Myocardial infarcts were found in one fourth of the cases in which autopsy was performed.

None of the 66 untreated patients recovered.

Recovery occurred in 2 per cent of 53 patients treated with sulfonamide compounds alone.

Two (15.4 per cent) of 13 patients adequately treated by combined chemotherapy and pyretotherapy were cured.

19. Spink, W. W.; Hall, W. H., and Ferris, V.: Clinical Significance of Staphylococci with Natural or Acquired Resistance to Sulfonamides and to Penicillin, J. A. M. A. **128**:555 (June 23) 1945.

There was no evidence that neoarsphenamine was of any value in the therapy of subacute bacterial endocarditis.

Of 12 patients treated with penicillin, 7 (58.3 per cent) have probably been cured. Reports to date would indicate that penicillin may be expected to be efficacious in from 65 to 70 per cent of cases of subacute bacterial endocarditis.

Continuous intravenous administration of penicillin was not satisfactory in the treatment of bacterial endocarditis because of frequent complications.

Continuous intramuscular administration of penicillin was a satisfactory method of treatment.

EDEMA OR HERNIATIONS OF FAT LOBULES AS A CAUSE OF LUMBAR AND GLUTEAL "FIBROSITIS"

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FIBROSITIS as a clinical entity has long been accepted in England, where it constitutes about 12 per cent of all medical cases seen. It has always been recognized, however, that its pathologic foundations are slender, resting as they do almost entirely on the theories of Gowers [1] and the observations, comparatively few in number, of Stockman [2] at the beginning of this century.

We were struck by the high incidence of this disorder amongst a large body of highly selected young men with whom we were in touch, and we made several careful attempts to remove and examine "nodules" which had been palpable to the examining finger through the skin. No areas of fibrosis were ever found, however, in this biopsy material, which in every case included muscle. These negative findings led us to seek a fresh approach to the whole problem, and our preliminary findings were summarized in detail recently.[3] These observations suggested that localized areas of fibrofatty tissue may for some reason, at present unknown, become edematous; and that owing to the unyielding nature of the fibrous investment in which they are enclosed painful tension is set up. It is believed that these observations afford the explanation for the pain in a certain proportion of cases of fibrositis of the back and the gluteal region, and that the pathology has not previously been described because abnormalities of the fibrofatty tissues as a source of pain have not yet received much attention.

It is not claimed that the views put forward here will cover all cases of fibrositis, which is in all probability a composite group. It is hoped, however, that they may lead to an extension of investigation on similar lines.

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1. Gowers, W. R.: Lumbago: Its Lessons and Analogues, Brit. M. J. **1**: 117-121 (Jan. 16) 1904.

2. Stockman, R.: Rheumatism and Arthritis, Edinburgh, W. Green & Son, Ltd., 1920.

3. Copeman, W. S. C., and Ackerman, W. L.: "Fibrositis" of the Back, Quart. J. Med. **13**:37-51 (April-July) 1944.

NATURE OF THE PAIN

As the result of the work of Sir Thomas Lewis and his school it has been accepted that the pain of fibrositis generally has its origin in certain focal points from which the subjective pain complained of by the patient is referred according to a segmental scheme. Such referred pain may be felt at a considerable distance from its real source, as is seen in cases of sciatica whose origin may be found in focal points situated in the lumbar or gluteal regions. These points are variously referred to as "trigger points," "myalgic spots," or "fibrositic nodules" when they are palpable. They are definite entities, since it is found that the patient winces involuntarily each time that the palpating finger exerts pressure there, while pressure of the same intensity exerted only a few millimeters distant will not produce the same response; a certain degree of more generalized deep tenderness may however be present and must not be confused. Pain in other areas which is being referred from a trigger point will generally be reproduced by the pressure, in addition to the local tenderness.

The treatment of these points by means of local anesthetic injections is, as is well known, often successful provided that the injection is made sufficiently accurately into the exact spot—not always an easy target.

One of us (W.S.C.C.) has recently observed that the pain in the back which accompanies many of the pyrexial illnesses such as influenza or the exanthems is of the same nature and pattern.[4] Is was shown moreover that, although the pain ceases with the end of pyrexia, in a proportion of cases unknown to the patient the trigger point will persist.

It is thought that this constitutes the basis of some cases of intramuscular fibrositis of the back which may occur at a much later date, when further infection or trauma reactivates the condition.

As will be shown later, these trigger points tend to occur in definite "sites of election" in the lumbar and gluteal regions (fig. 1), and they correspond in the cases to be described, with protrusions of fibrofatty tissue, squeezing of which reproduced the pain, and removal of which relieved the patients of their pain and tenderness.

SITES OF THE PAINFUL SPOTS

Trigger points have been mapped out in a large number of fibrositic patients, and their situation carefully plotted. The result of this in a series of 65 unselected cases is shown in figure 1. This might be termed the "pain pattern."

From above downward the situations in which a majority of these points cluster are: the point where the outer edge of the sacrospinalis

4. Copeman, W. S. C.: Aetiology of the Fibrositic Nodule: A Clinical Contribution, Brit. M. J. **2**:263-267 (Aug. 28) 1943.

muscle meets the posterior costal margin; a spot about 2½ inches (7.4 cm.) above the iliac crest, which is the level at which the latissimus dorsi muscle often crosses the edge of the sacrospinalis muscle; another spot an inch (2.5 cm.) lower, and another at the edge of the sacrospinalis muscle just above the iliac crest. In the gluteal region these points may be found all along the crest of the ilium and for a distance of about 2 inches (5.1 cm.) below it. They may also be found along the sacroiliac junction where the deep fascia is attached. They are much less commonly found elsewhere in the buttock.

ANATOMY OF THE NORMAL BACK

Fourteen backs were dissected with special reference to the areas shown in figure 1, which were the commonest sites for the occurrence of fibrositic trigger points.

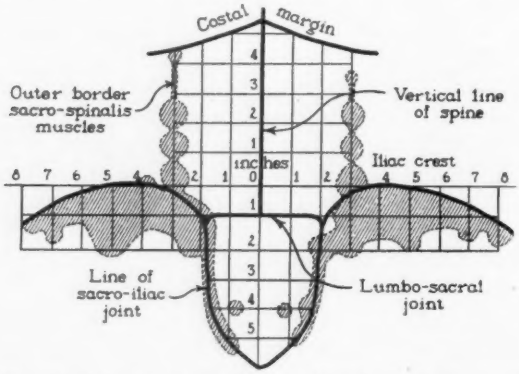

Fig. 1.—The shaded area shows the location of the "trigger points" in 65 consecutive cases of fibrositis.

In the standard textbooks of anatomy not much information can be gained regarding the relationship of the fascial layers of the back with the body fat. The following brief description of our findings seems therefore to be justified.

Deep to the subcutaneous fat and areolar tissue lies a highly vascular sheet of fascia which stretches from the neck to the gluteal region. For most of its area the space between this and the deep fascia is only a potential one, containing little or no fat. In certain well defined places, however, deposits of pinkish fibrofatty tissue occur regularly, and it is these regions, together with the equally constant deep ones to be described, which constitute what we have called the "basic fat pattern" (fig. 2) in view of its constant occurrence even in the most grossly wasted bodies, in which most of the body fat elsewhere had disappeared.

In obese persons this fat pattern tends to become obscured owing to the more generalized deposition of fat.

It was noticed that the fasciae were not of uniform thickness everywhere, being noticeably thinned in certain places, while actual deficiencies were not infrequently found. In these places if fat was lying underneath it tended to bulge through the fascia, and a complete herniation of such fat was sometimes seen.

THE "BASIC FAT PATTERN"

In the lumbar region the sacrospinalis muscle is edged with a strip of fat lying within the angle made by the deep fascia as it splits to enclose this muscle. There is also what may be called the "lumbar fat

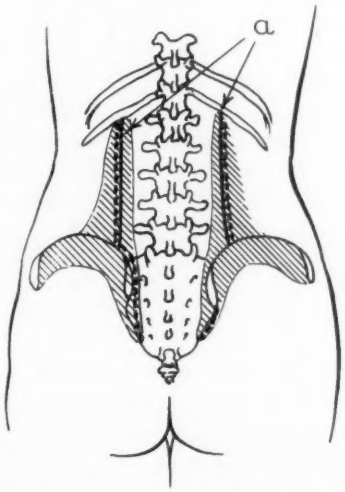

Fig. 2.—The "basic fat pattern." This appears to represent the irreducible minimum of fat in the back under any condition. The dotted lines represent the deeper portion contained in the fascial angle along the outer edge of the sacrospinalis muscle. The letter (*a*) indicates edge of sacrospinalis muscle.

pad," which is a collection of fibrofatty tissue which lies more superficially in the same region. Along the sacroiliac junction there is also a tongue of similar fibrofatty tissue which follows the attachment of the deep fascia and the muscle.

Careful dissection through the lumbar fat pad revealed that it is at the two lower points of maximum tenderness along the edge of the sacrospinalis muscle (fig. 1) that the cutaneous branches of the posterior rami of the last three lumbar nerves pierce the deep fascia, after leaving the body of the muscle. This they appear to do through definite foramens and accompanied by small blood vessels. In 2 of the bodies

dissected a small tuft of fat lobules was protruding through the foramen of the third lumbar nerve in addition to the nerve and blood vessels, probably as the result of postmortem pressure. There is a small horizontal fold of the deep fascia overhanging each foramen, which would seem to be designed to prevent this protrusion of its contents during life by acting as a valve to occlude the foramen on flexion of the back. As the result of the observations recorded later it is believed that these valves do not always perform this function efficiently, and that failure to do so will allow such herniation to occur in the living subject. This may be a cause of sudden acute lumbago which occurs as the result of weight lifting in the stooping position.

In the gluteal region there is a crescent of pinkish fibrofatty tissue which lies along the crest of the ilium and for a distance of about 2 inches below this (fig. 2). It is contained within the layers of the superficial fascia and extends from the anterior superior spine back to the sacroiliac junction, after sending a narrow prolongation down along this region, as shown in figure 2. This lies at a more superficial level than the similar tongue described earlier.

It is not uncommon also to see small "bubbles" along the fascia edging the sacrospinalis muscle, caused by bulging of fat lobules which are contained within the angle of this fascia where it splits to enclose the muscle. These represent weak spots in the fascia, and firm pressure applied immediately adjacent to one of these potential hernias in the cadaver will generally convert it into a fat hernia of the size of a pea or larger.

CLINICAL OBSERVATIONS

To supplement the 10 case histories already recorded,[3] we wish to report here 11 new cases which illustrate the clinical importance of the anatomic observations just discussed.

The therapeutic success which attended the result of the biopsy in every case supports the view that the herniation of fatty tissue through the fibrous fascial compartment in which it was lying was causative of the pain complained of by the patient.

REPORT OF CASES

CASE 1.—*Foraminal Type of Hernia.*—H. H., aged 42 years, had had no serious illness. Fifteen years before (1928) he had an appendectomy under general anesthesia; since then he had had almost continuous backache. This was worse after severe exertion or when he was tired. If he caught influenza or a cold his back became painful during the febrile period. He had had much massage and other physical treatment.

On examination a tender spot was found at the border of the right sacrospinalis muscle 1 inch above the iliac crest. This was transfixed at a depth of 1¼ inches (3.2 cm.). An incision was then made, and the deep fascia was exposed. A small lobule of reddish fat was found to be herniating through a patent nerve foramen at

this point. This was removed—reproducing the pain during the process—and the foramen was enlarged to prevent the possibility of "strangulation" in the event that further fat lobules herniated. The lobule was found to be continuous with the deep basic fat, lying in the angle of the fascia, where it splits to enclose the muscle.

The patient had no subsequent recurrence of pain in this region.

CASE 2.—*Nonpedunculated, Lateral Type of Hernia.*—L. P., aged 30 years, had had severe pain in the left buttock and down the back of the thigh for one year. The original cause was not known. No history of injury or infection was obtained. The pain was most severe when the patient lay in bed. It flared up with an episode of infective hepatitis.

On examination a tender nodule was found in the left buttock. Pressure on this reproduced the pain, which ran down the back of the left thigh to the ankle. All reflexes were normal. Procaine hydrochloride, 10 cc. of a 1 per cent solution, was injected, and the area was "teased" with a thick needle. This definitely improved the condition, but the nodule was still tender and the patient was anxious for permanent cure.

An incision was made over the nodule, and layers of fat in the superficial fascia were cut through. In the second or third layer some tense lobules bulged up into the wound when their septums were cut. One of these, which was the size of a large pea, was removed. The remainder were "teased" and broken up. A definite cavity was left. This fat was superficial to the fascia over the gluteus maximus muscle.

Ten days later the patient was free from pain, and a small hematoma under the scar was aspirated. The pain had not recurred when the patient was seen six weeks later.

CASE 3.—*Nonpedunculated, Lateral Type of Hernia.*—Q. M., 49 years, had had sciatica on the left side for five months. Onset was sudden. The cause was unknown. No history of severe exertion was obtained. It was worse when he lay down in the damp. He had been working hard in his office and thought that he was "run down." Many subcutaneous abscesses developed.

We first saw this patient after he had been in the hospital for ten days for these abscesses. He looked ill and wasted. He had severe pain in the right buttock, radiating down the back of the thigh into the calf and the ankle. Lasègue's sign was strongly positive. Coughing exacerbated the pain. All reflexes were present, and sensation was normal. The roentgenologic examination revealed no bony disease of pelvis or lumbar portion of the spine. There was a definite tender nodule in the left buttock, pressure on which caused pain down the back of the leg to the ankle. Physical treatment and complete rest were employed for three weeks, but the patient still complained of pain and the nodule in the buttock was tender.

A small incision was made into the deepest layer of superficial fascia, and, directly under the site of the maximum tenderness, an edematous fat lobule under tension bulged into the wound. When it was grasped firmly with forceps, but not pulled, it caused the sciatic pain. This lobule was removed, and septal walls were broken down. A large space was left, and hard pressure did not reproduce the pain. He was subsequently free from pain down the leg but had some local soreness of the buttock for two weeks.

CASE 4.—*Deep Nonpedunculated Type of Hernia.*—G. W., aged 32 years, had had backache every winter for five years. In 1943, he was laid up for a week or so with an attack of sciatica on the right side. He was treated in hospital with massage

and rest. Early in December 1943, the pain returned three days after resumption of duty, and persisted in spite of massage and injections into the buttock. Local injection of procaine hydrochloride on readmission reproduced sciatic pain and did not give relief subsequently.

On admission the patient appeared well nourished and had severe pain in the right buttock and down the back of leg into the calf. Lasègue's sign was positive. Definite tender nodules were felt in the right buttock, and pressure on them reproduced the pain down the leg.

Vertical incision was made over the nodule. At first, no abnormality was found. The deep fascia was then exposed and incised, directly under the site of original tenderness. Immediately the patient said, "That's it." A deep compartment containing fat was found to have been opened, and the tense fat, which was the size of a marble, was removed. Septums of fat compartments around this now empty space were broken down by pressure of the finger, and the wound was closed. Next day, the pain had completely disappeared from the buttock and down the thigh. Some pain still remained around the ankle. The patient was encouraged to walk as normally as possible. A week later he still had no pain in the buttock and back of the thigh, but after walking he had a dull uncomfortable feeling in the right ankle, calf and right knee, which lasted for several weeks, but finally disappeared.

CASE 5.—*Nonpedunculated Interseptal Hernia.*—L. B. N., aged 38 years, had had sciatica on the left side for ten weeks. He had been in various hospitals, where he had had injections of nupercaine hydrochloride, sometimes with mild transitory relief. The sciatica was made worse by cold and movement. The pain was severe and shot down the thigh and calf to the heel; it also extended into the left groin. No cause was found. He had had no previous fibrositis or rheumatism.

On examination Lasègue's sign was positive. Some diffuse tenderness was found in the left buttock, and one definite palpable nodule was found, pressure on which caused pain down the thigh. Tender spots were found also at the outer border of the left erector spinae, but no pain was referred from these.

Fat in the superficial fascia of the left buttock was incised. It was extensive, with thick interlobular septums down to gluteal fasciae. The latter looked normal and were not incised. Nothing was at first found until a tense fat lobule, lying directly under the original point of tenderness at a deeper level than had been anticipated, was grasped by the forceps, reproducing immediately the original pain in its whole distribution.

A lobule of edematous-looking fat about the size of a small cherry was removed. No obvious herniation through fascial tissue was discovered.

A week later the patient stated that he had lost all the pain down the thigh as the result of the operation, but that he had still a dull aching pain in the calf. This gradually improved, and a month afterwards he was able to be back at full duty.

CASE 6.—*Pedunculated Fat Hernia.*—A. H., aged 30 years, had suffered for sixteen years with a severe pain in the lower part of the back which had been present ever since he had had a skiing accident and fallen sharply onto that side. The intensity of the pain varied, being worse if he had any mild infection, and in cold weather. He had sometimes to stay in bed on account of it. Physical treatment always made it worse, as did excessive exercise.

A tender nodule was palpated just below the iliac crest and about 4 inches (10.2 cm.) from the midline. An incision was made over this, and a congested-looking lobule of fatty tissue was found lying superficial to the deep fascia, with

a pedicle leading down through the fascia. The pedicle was traced downward and eventually disappeared into the deep layer of fibrofatty tissue which was lying at a deeper level. Two small blood vessels accompanied its course.

Compression of this lobule reproduced the patient's complaint. Hence the lobule was removed. Seen a month later, the patient said that his pain had not recurred and that he considered himself cured.

CASE 7.—*Nonpedunculated Fat Hernia.*—S. M. C. aged 26 years, about four years previously had acquired a severe backache while doing some strenuous exercises. This passed off after a few days with physical treatment. This pain had recurred from time to time, more particularly when he was in poor health. He was seen by us at a time when the pain was particularly bad. A tender nodule could be palpated on the edge of the right sacrospinalis muscle about 1 inch above the iliac crest.

An incision was made with the patient under local anesthesia, and the fat incised down to the level of the border of the muscle. Two "bubbles" of thin fascial tissue were seen at this site, and on incising them a few lobules of fat under considerable tension welled up out of them. On incising the fascia which lay between them it was seen that there was a band of thick fibrous tissue, forming part of the deep fascia, which appeared to have been constricting the base of the fat lobules and so probably accounted for their swelling.

The patient lost his pain as the result of this procedure, and in spite of severe testing it had not reappeared when he was last seen six weeks later.

CASE 8.—*Fat Under Increased Tension, as Result of Old Hematoma, Giving Rise to Pain.*—N. B., aged 33 years, had complained of "lumbago," generally on the left side, for the last two years. Onset was with strain caused by lifting a heavy weight onto his back.

Pain was present most of the time but varied in intensity. When it was bad, the whole back was painful. He had no previous rheumatic complaints. He had had much physical treatment with temporary benefit only.

The patient was heavily built and was of a somewhat plethoric type. A tender palpable nodule was felt towards the midline, opposite the fourth lumbar vertebra. It was about the size of a pea. Surrounding skin was thick and puckered when pinched. Deep pressure reproduced the pain.

An incision was made over the nodule. Subcutaneous fat was divided into compartments by thick fibrous septums. The "nodule" was found to be a tense lobule of fat in such a compartment, and on dividing fibrous tissue it was found to be under considerable tension. A small collection of brownish fluid was also present and was suggestive of an old hemorrhage into the fat lobule.

The cause of the pain here was not herniation, but increased tension in a fat lobule, due probably to trauma in the past.

CASE 9.—*Compression of a Fat Lobule by Deep Fascia.*—Three years ago, P. S., aged 33 years, had pain in the lower part of the spine and the right thigh. Electric treatment and massage were given, and the pain disappeared in a week. Ten months ago the pain recurred after strain. Pain was severe and left him "stooping" for three weeks. For three months he was free from pain, but it recurred when he was lifting a heavy table. Massage and electric treatment gave improvement until two months ago, when pain got severe again and he was readmitted to the hospital. Several injections of procaine hydrochloride gave transient improvement.

On examination pain was severe, and it commenced in the right buttock and traveled down back of the thigh into the calf. It was worse on coughing and on

moving. The patient had difficulty in bending forward at all. Lasègue's sign was positive on the right side. Reflexes were normal. A definite tender spot was found 2½ inches from the midline, and 1½ inch (3.8 cm.) below the iliac crest. Pressure there caused acute pain down the leg.

A vertical incision was made, and fat was found in layers of the superficial fascia, but no definite herniation was encountered. The deep fascia over the gluteus maximus then was incised, with relief of the pain. Beneath this between the digitations of the gluteus muscle were small "fingers" of fat which passed downward through the deep fascia from the superficial fat. It seemed that these were being compressed between this thick fascia and the bone of the sacroiliac ridge. The deep fascia was left gaping, but the fat was not removed.

Two weeks later sciatica had disappeared and had not returned. Some local tenderness was present in the lower fold of the buttock; otherwise the patient felt fit. One month after operation the sciatica had not returned.

CASE 10.—*Nature of Fat Lesion Uncertain.*—S. V., aged 46 years, a well nourished prisoner of war, for three months had had pain in the lower part of the back shooting down the back of the right leg.

On examination there was a definite tender spot over the right edge of the sacrum. Pressure here caused pain down the leg. Less definite tender spots were found in the right buttock also.

A vertical incision was made over the tender point on the right side of the sacrum. The superficial fascia and its contained fat layers were incised down to the fascia over the sacrospinalis. No apparent herniation of fat was noted, but fat in the superficial fascia was thoroughly teased.

Two days later the patient stated that he was cured, for he had no pain whatever on any movement. This prisoner had every reason for not saying that he was cured, as the hospital was more comfortable than the prison camp to which he was discharged. One month later, when the patient was seen in the camp, he still maintained that he was cured, although he stated that he was unhappy there. This was considered proof of the success of the procedure.

CASE 11.—*Fat Hernia of the Direct Nonpedunculated Type.*[5]—S. T., aged 39 years, had no family history of rheumatism and no previous history of any disease other than usual fevers. The onset of pain in the region of the iliac crests was gradual during the last five years but it was most localized and intense on the right side. He had suffered with benign tertian malarial relapses on several occasions during this war, and during these attacks the "lumbago" became much worse. Deep massage at first exacerbated the pain and later generally helped it considerably.

This patient was in the hospital with a malarial attack when we first saw him. He was found to have hard palpable "nodules" on each iliac crest, two of which were exquisitely tender on pressure. Roentgenologic examination of the lumbar spine revealed early osteoarthritis.

An incision was made through the gluteal fat which lay over the tender area. At a depth of about ½ inch (1.3 cm.) a spherical encapsuled "bubble" of tense pinkish fat was found lying under the other fat layers. On palpation it felt hard and reproduced the patient's pain. Squeezing it, without producing tension on its root, caused definite pain. Its removal cured the patient's pain (fig. 3).

5. Major J. Charnley, F. R. C. S., carried out the operation, and Major F. Brockelbank furnished the photograph.

CLINICAL PATHOLOGY

As the result of biopsies performed on these and other sufferers with "fibrositis" it was found that the trigger points or tender nodules which are characteristic of the disease corresponded in all the cases recorded with herniations or protrusions of edematous fat lobules through deficiencies in the walls of their fibrous compartments.

It was found possible to classify these fat hernias into three anatomic types: (*a*) the pedunculated, (*b*) the nonpedunculated and (*c*) the foraminal types (fig. 4). These names are self explanatory, and a fuller description was previously given.[3]

Microscopic examination of the herniated fat lobules removed at biopsy showed them to consist almost entirely of fat which showed evi-

Fig. 3.—Bubble of fat removed in case 11.

dence of edema as its only abnormality. In no case was there evidence of recent inflammatory reaction such as a cellular exudate, although the blood vessels were congested, and in some cases their walls appeared to be thickened. In 3 cases small areas of young cellular fibrous tissue were seen to be growing into the fat, and in the cases of the pedunculated type patches of older fibrous tissue were seen affecting the base of the pedicle, as might be expected.

Owing to the exigencies of active military service we were unable to stain sections for nerve endings.

From the general nature of our approach and as the result of subsequent (unpublished) work it gradually became evident to us that these fat herniations represent a comparatively advanced stage of the disease

process, and that the minor and less localized degrees of pain which are so common as to be almost universally experienced at some time or other may depend on a temporary increase in the fluid tension in the tissues affected, of which the basic cause is so far unknown. When this process has repeated itself sufficiently often, and when the situation is anatomically suitable, actual protrusion of the tissues commences to occur, with the ultimate formation of the herniations which we have described.

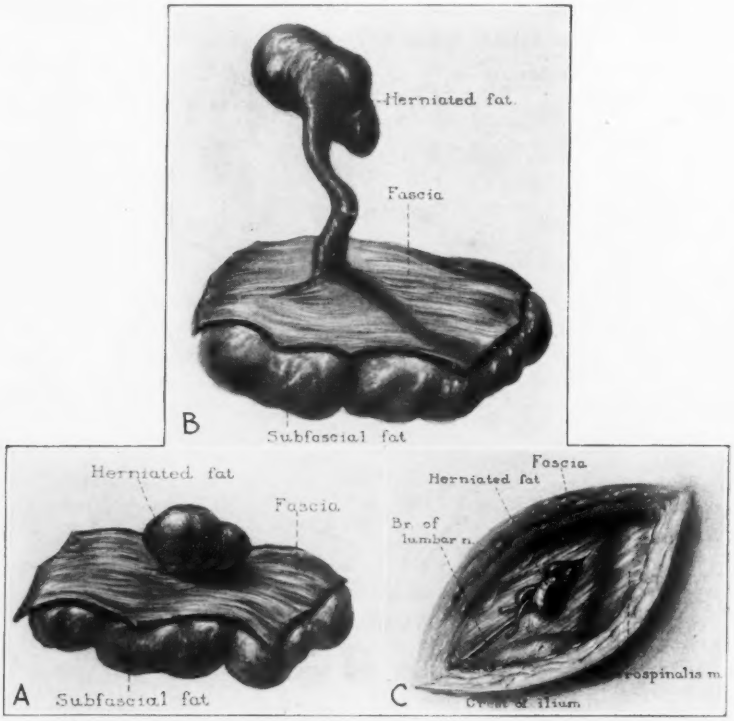

Fig. 4.—*A*, the nonpedunculated type of fat hernia. *B*, the pedunculated type of fat hernia. *C*, the foraminal type of hernia.

PANNICULITIS

As the result of the conclusions which we had reached from our study of the back and the gluteal region it was decided to investigate some cases of that type of fibrositis which occurs around the knee joints chiefly in women who are within the menopausal age zone.

Our observation of this syndrome had suggested that at that period of life fat is normally laid down in this location and that in cases in

which pain developed some abnormality of this fat might be found to be responsible.

We have explored these fatty deposits, when they had become painful, in 6 patients of this type. The fat was found throughout to be divided by firm fibrous septums into small compartments, each containing a few lobules. These took their origin from the subcutaneous region of the skin and passed inward to blend with the deep fascia which invests the vastus internus muscle.

On dividing the walls of these compartments in the painful regions the contained fat lobules immediately bulged out to an extent that suggested that their tension was abnormal. In areas which had not been painful this tension did not appear to be nearly so high.

Careful examination of the affected regions did not reveal any example of herniation of these lobules into neighboring compartments; indeed the walls appeared mostly to be too thick for this to have occurred except with great difficulty.

The therapeutic effect of the division of these fibrous septums over a considerable area was to relieve the patient's pain permanently in 4 cases, while the other 2 reported considerable relief subsequently. Therefore it appears to us that the tension in the fat lobules, which was released as the result of our exploration of the affected regions, might have been associated with the previous pain. It is realized that other explanations could be suggested.

It could not be said with confidence whether the apparent increase of tension in the fat lobules was the result of positive swelling in the fatty tissues, or of contraction of the fibrous elements. However, in view of the variability of the pain, which was affected by such factors as cold or variations in weather, it seemed more probable that the pain was dependent on some variable process such as edema. If this is so, the mechanism already postulated as to the cause of pain in certain cases of fibrositis of the back and gluteal region could also be suggested as being operative in the case of periarticular fibrositis ("panniculitis") of the menopausal type.

THERAPY

The operative procedures in these cases were undertaken chiefly for the purposes of investigation. Although these surgical procedures did cure the patients, we do not advocate them in most cases because we believe that relief can be afforded by other, less drastic measures. We believe that the pathologic conditions described can be shown to have some direct association with several methods of treatment which at present rest on an empiric basis.

Heat, Massage and Movement.—The pathologic basis offered in this paper for the cases of fibrositis described would appear to place these

traditional methods of rheumatic treatment ("the therapeutic tripod") on a scientific footing for the first time. It is reasonable to aim at increasing, by means of heat, the local blood supply and so the drainage from an area which is the seat of gradually increasing congestion, edema and tension.

In the early stages of herniation of the fat lobules, it is equally reasonable to endeavor to "reduce" them by massage, to force the accumulated edema fluid into the lymph drainage channels, and later when they are no longer reducible, owing to adhesions to neighboring lobules, to break them up by mechanical pressure. It seems evident that it is in this way that the disappearance of "fibrous nodules" as the result of massage can be explained.

The rationale of active muscular movement is that it is the essential factor for the efficient functioning of the lymphatic system, and in early cases in which the lesion is still reversible active muscular movement is found to be helpful. It is the common experience that the condition is worse while the patient is lying in bed or after a night's rest.

Injections of Procaine Hydrochloride.—These would seem to be able to act in two ways. In those cases of sudden onset, (e. g., lumbago), which are believed to be due to the sudden herniation of a fat lobule through one of the lumbar nerve foramens or in the basic fat pattern in the superficial fascia, the anesthetic action will relieve the pain for sufficiently long to allow a resumption of muscular movement, which may be sufficient in itself to reduce the protrusion.

More commonly the correct objective of this type of treatment would seem to be to disrupt the fat "nodule" by hydrostatic pressure, and so relieve the local tension on which the pain appears to depend. It is for this reason that such accuracy in making these injections is essential.

"Teasing."—Since we have observed the nature of the "fibrositic" lesion at biopsy, we have evolved a rather different technic, which we refer to as "teasing" the nodule. This process consists in anesthetizing a small area of skin over the site of the trigger point, which has previously been ringed with a skin pencil. The nodule is then transfixed through this area, with a stout rigid "record" needle. After 10 to 20 cc. of 1 per cent solution of procaine hydrochloride is injected under the greatest pressure possible, the cutting point of the needle is swept around deeply in such a way as to "undercut" the nodule, much as a tenotomy knife might be used, in an attempt to divide the pedicle of the herniated portion should there be one and to disrupt also any neighboring lobules which may be sharing in the congestion.

By the use of this method, which must be tempered with at least an elementary knowledge of the anatomic formation of the area being

treated, we have achieved more lasting results than with the normal technic of injection.

SUMMARY AND CONCLUSIONS

A systematic study of fibrositis of the lumbar and gluteal regions has been made in a body of picked men. The pain has been studied clinically, and we have confirmed the occurrence of localized "trigger points" from which pain in this condition may be widely referred. The exact situation in which these occurred in a series of patients was charted, and a "pain pattern" of definite shape resulted.[6]

Our previous observation that these points may arise during any pyrexial illness, or as the result of trauma, was confirmed; also that the subjective pain often disappears, but that the point remains and can be detected by its tenderness on palpation. It can be reactivated subsequently, and may gradually become the seat of chronic pain.

The back was carefully dissected in 14 bodies with particular reference to the sites at which pain had chiefly been found to occur. It was found that a "basic fat pattern" was constantly present, even in the most cachectic subjects, in whom all other fat was absent. This "fat pattern" was observed to correspond with the "pain pattern" already charted, in situation and shape.

Our observations show that the production of pain at these trigger points takes place in certain fibrofatty tissue, and not in the muscles, as has often been stated. The local lesion demonstrated in those cases in which biopsy was performed consisted of an increase in the volume of certain fat lobules in situations where expansion was normally limited by an unyielding fibrous capsule. In one case (case 8) this increased tension in the lobule appeared to be the result of an old hematoma.

In the clinical cases described in this paper this process had progressed further, and actual herniation of these lobules had occurred through weak spots in the fibrous compartment or capsule. The causative nature of these lesions seemed to be confirmed by the patient's freedom from pain subsequent to the removal of the herniations.

Exploration of the painful area in a small series of cases of periarticular fibrositis ("panniculitis") of the menopausal type suggested that a similar mechanism might also be responsible for the pain in these cases.

Physiologic principles underlying certain lines of physical treatment commonly employed in the treatment of fibrositis are shown to be rational for the pathologic conditions described.

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6. Major W. H. Mylechreest, R.A.M.C., provided postmortem facilities and also cut sections of the biopsy material. Dr. Philip Hench of the Mayo Clinic gave assistance and advice in the preparation and presentation of the manuscript.

SCHISTOSOMIASIS JAPONICA WITH CEREBRAL MANIFESTATIONS

Report of Seven Cases

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ABOUT two to three months after the American forces occupied the province of Leyte, in the Philippine Islands, cases of early schistosomiasis japonica were encountered. This report is concerned with a group of unusual complications of this disease. These cases constitute a bizarre picture of an exotic disease, but when they are grouped together a syndrome emerges which can be recognized clinically. Experience in the Far East indicates that in view of the immediate severity as well as the residua of the disease this group is sufficiently important to merit study.

Schistosoma japonicum, like all other trematodes, has a life cycle which includes parasitic infection of an intermediate host prior to the development of the adult worm found in man. The egg, passed from the human or the animal host, quickly hatches a miracidial larva in the fresh water of streams and rice paddies. The free-swimming miracidia seek out a suitable snail of the genus Oncomelania (in these cases). After the miracidia have developed for several weeks in the snail, sporocysts containing cercariae are formed. These are released into the water daily in large numbers. On contact with the skin of man and of other mammals, they quickly penetrate and gain entrance by way of capillaries into the systemic circulation. It is said that only those parasites which arrive in the intrahepatic circulation survive. The majority of worms migrate to the finer radicles of the mesenteric vessels, where they mate and produce ova, but some authors have mentioned the presence of mature worms in the pulmonary vessels. The development of the cercaria into the adult worm requires from five to eight weeks.

A discussion of the relationship of the parasite to the production of symptoms may aid in their recognition. The time of appearance, the character and the site of symptoms vary with the degree of infection, the development (cercaria, mature worm, ova), the toxic or the mechanical effects of the parasite and the reaction of the host.

The cercarial or larval phase lasts a few weeks. Its effects on the skin are immediate, and the reaction may result in localized eruption.

Within two or three weeks after penetration of the skin the filter bed of the pulmonary vascular tree in turn becomes the site where large numbers of young worms exert their effects. A patchy pneumonic involvement may result. So far this stage has not been recognized clinically, since the patients come under observation some time after the pulmonary episode. However, a history suggesting just such an event is frequently given. It is quite possible that this reaction persists for six to twelve weeks after infection, since cough and diffuse pulmonary roentgenographic shadows are present at the time of the initial observation.

The mature fluke deep in the mesenteric radicle probably produces little subjective disturbance, for asymptomatic patients passing ova are encountered occasionally and a long asymptomatic period is noted between the acute and the chronic stage of the disease. Collections of ova in tubercle formation gradually work their way into the intestinal lumen and cause pathologic changes varying from fine scarring to massive distortion of the intestinal structure. The association of symptoms in this process appears clear, and the severity varies with the degree of destruction. In addition to local effects at the site of their production, ova produce far distant involvement through embolic distribution. Ova produced in vascular radicles drained by the portal vein, in addition to penetrating and damaging the liver, may gain entrance to the systemic circulation by way of collateral channels through the hemorrhoidal plexus and eventually reach the lung. The lung becomes the site of multiple areas of ova and their attendant reaction, which occasionally includes small thromboses and necrosis of tissue. Some ova break through and by way of the bronchial artery and pulmonary vein collateral plexus enter the systemic circulation and are swept to distant organs. This mechanism need not be invoked if there is a cardiac septal defect. Day (quoted by Stitt),[1] describing Schistosoma mansoni, stated that rarely adult flukes migrate and are carried to the pulmonary arteries. Although I have no evidence to date that such migration occurs with S. japonicum, as there were no deaths in this series, it must be considered a possible source of metastatic ova. While the means and the pathway of the distribution of ova may not be established, it must be remembered that ova may be found in any organ. It is interesting to note that the scanty bibliography available mentions similar cases in which the disease is attributed to ova deposited in the brain and the spinal cord.

Faust and Meleney[2] stated that Yamagawa, in 1890, mentioned jacksonian epilepsy occurring in a patient with schistosomiasis japonica,

1. Strong, R. P.: Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases, ed. 6, Philadelphia, The Blakiston Company, 1942.

2. Faust, E. C., and Meleney, H. E.: Studies on Schistosomiasis Japonica, Baltimore, American Journal of Hygiene, Monograph Series, 1924, no. 3.

and that Houghton, in 1910, also described a case in which he suspected that symptoms referable to the brain were due to deposits of eggs. They stated that such cases are rare. Spiridion [3] described an outbreak of schistosomiasis japonica in China. Three patients showed neurologic involvement. The first patient was semicomatose and incontinent; bilateral ptosis, flaccid paralysis of the upper limbs and exaggerated reflexes and clonus of the lower limbs were present, while the colloidal gold test showed the curve characteristic of dementia paralytica. The second patient had delirium and coma lasting four weeks, screaming alternating with sleep, trismus, retraction of the head, opisthotonos and Kernig's sign, spasticity of the upper extremities, exaggerated knee jerks and clonus. The spinal fluid contained no cells and the colloidal gold test gave the curve characteristic of dementia paralytica. The third patient presented flaccid paralysis of the left upper and lower extremities, with diminished reflexes. These authors stated that jacksonian epilepsy and hemiplegia had been reported by others. Stitt [1] and Manson [4] mentioned that, in addition to fits, hemiplegia and total blindness may occur after ova have been deposited in the brain.

The cases which I shall report were collected in a hospital functioning and undergoing construction simultaneously during the peak load of the Philippine campaign; it was understaffed and overcrowded, and the laboratory facilities were overburdened. During this time medical care was necessarily and primarily concerned with returning the soldiers to duty. The patients were handled routinely and not in the light of a future report. Only because of the severity of the illness of these patients were notes and laboratory data somewhat more detailed than customary. During this period schistosomiasis assumed epidemic proportions among troops. Six patients with cerebral manifestations were observed among 181 patients with schistosomiasis admitted to the hospital from January 15 to July 15, 1945. An additional patient (case 1) observed at another hospital on the island of Leyte is included.

These soldier patients were aged from 20 to 29. All of them had landed on Leyte for the first time during the interval from "D" Day, Oct. 20, 1944, to Dec. 25, 1944. All of them had been exposed to contaminated water, subsequently proved by survey to contain infected snails. Six soldiers were white, and 1 was Negro. It is not possible to determine whether race played a part in this discrepancy or whether it was a result of the numerical difference of troops. All were healthy and combat fit prior to their illness.

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3. Spiridion, J. T.: Schistosomiasis Japonica: An Account of an Outbreak, J. Trop. Med. **39**:161, 1936.

4. Manson-Bahr, P.: Manson's Tropical Diseases, ed. 11, London, Cassell & Co., Ltd., 1942.

REPORT OF CASES

CASE 1.—A white soldier was admitted on Jan. 9, 1945, with a diagnosis of encephalitis. He had landed on Leyte, Oct. 20, 1944. He washed and swam in various streams. One of his camp sites had been flooded out early on his arrival. About three weeks before admission he had a "febrile" illness, for which he did not seek medical attention and which he described vaguely. On January 8 he became weak in all his extremities and was sent to the hospital the following day. Examination showed that he was obese, febrile and acutely ill; there was flaccid partial paralysis of both arms and legs with ataxia; all deep and superficial reflexes were present; there were no sensory disturbances; both the great toes and the small toes were discolored and tender. The following day a spinal tap obtained fluid not under increased pressure, containing 12 cells per cubic millimeter; the Pandy test was negative. The abdominal reflexes were absent, and the cremasteric reflexes were just obtained. He became confused, incontinent and restless and answered questions with difficulty. He was unable to focus his eyes and moved his legs incoordinately. Three days after admission, January 12, he had regained some control of the bladder, was disturbed, confused, anxious and complained of painful feet, which were blotchy and purple, particularly the small toes and the plantar aspect. The next day, he was slightly disoriented. Save for loss of convergence, the cranial nerves were intact. The sensorium was intact; there was weakness as well as spasticity of all extremities, with left patellar and ankle clonus. Extension and flexion of the left arm were minimal, and finger extension was absent. The cremasteric reflexes were barely present, there was exaggeration of all deep reflexes with Babinski's reflex positive on the left side and equivocal on the right. The feet were cool, and pulsation of the popliteal and posterior tibial arteries was normal. The total leukocyte count was 27,400, and the eosinophils were 38 per cent. On January 14 the left pupil was dilated, but on January 15 the pupils were normal. The heart and the lungs were normal, the liver was slightly enlarged, firm and not tender, and the spleen was not felt. The patient was less confused. The muscle strength of both arms was 25 per cent of normal, and that of both lower extremities, slightly diminished. The discoloration of the feet was less than it had been forty-eight hours previously; the distal half of the nail of the left index finger also had acquired a bluish discoloration. The hyperreflexia was unchanged; there was sustained patellar and ankle clonus on the left side and nonsustained on the right side; the Babinski reflex was absent. On January 17, additional bluish-discolored lesions were noted on the calves of both legs. The patient was still mentally disturbed. The stools contained ova of S. japonicum. Fuadin therapy (50 cc. of fuadin, containing 0.42 Gm. of antimony) was started and completed on February 4. On January 18 spasticity was less; the pupils were again unequal; confusion and irritation were less, and the temperature, previously ranging between 99 and 100.6 F., became normal. A biopsy specimen taken from the discolored area of the right calf showed skin exhibiting perivascular inflammatory infiltration, vascular changes and thrombosis, with no specific etiologic agent discernible. Two days after therapy, January 19, the patient was clear mentally; the right pupil was dilated in the morning, but at 3 p. m. the pupils were equal and regular and reacted promptly to light. Convergence was still weak. The arms, still spastic, were stronger, but the right forearm was paretic; coordination was poor, and there was sustained patellar clonus, but ankle clonus was transient. Three days after the start of fuadin therapy, January 20, improvement was unmistakable. The patient sat on the side of the bed for a short time. Fluid had

collected under discolored areas of the heels, and the toes had cleared except for the tips, which were still deeply purple. One week later the muscle power of the arms had increased, and ankle clonus was transient; mild diplopia was present. At the end of the course of fuadin, February 4, an ambulatory status was reached; hand motion was better, but there was still incoordination of the arms, and ankle clonus was not present. Five days later, on February 9, Babinski's reflex and clonus had returned on the left side, and the tips of both small toes were necrotic. These areas gradually became demarcated in the course of the next week, when it was noted, February 15, that his condition was excellent in comparison with what it had been on admission. The following day he was transferred to another hospital.

Summary.—Two to three months after exposure this man suffered from quadriplegia, confusion, disorientation, pupillary changes, paresis of the abducens nerve and incontinence. Recovery was slow and incomplete one and a half months later. Leukocytosis and eosinophilia were evident. Ova of hookworm and S. japonicum were demonstrated.

CASE 2.—A 25 year old Negro soldier was admitted to the hospital on Jan. 24, 1945, complaining of "swelling of the face, the hands and the abdomen."

He had landed on Leyte on Nov. 15, 1944, two months prior to admission. He said that he had not been swimming in fresh water streams but he had washed trucks in the river from December 20 to Dec. 25, 1945, inclusive. He had waded through rice paddies on innumerable occasions. One week before admission he had a cough which lasted for four days and was productive of yellowish phlegm. Three days before admission he suffered from anorexia, weakness, generalized aches and soreness, and both feet felt "dead." Two days before admission an itching eruption developed on the face, the hands, the chest and the abdomen.

Two members of his organization, who worked with him, were in the hospital with schistosomiasis, proved by examinations of the stools.

One aunt of the patient had tuberculosis.

The patient was born in South Carolina. Syphilis and gonorrhea had been contracted three years ago. He had been treated for eighteen months and had several negative serologic tests prior to and after entrance into the Army. Many years previously he had an attack of hives.

Examination disclosed moderate circumscribed edema of the wrist and the flexor surfaces of both arms and slight puffiness of the eyes and of the fingers of both hands. On the lower part of the chest and on the abdomen there were several circumscribed, various-sized, urticaria-like areas. The blood pressure was 110 systolic and 70 diastolic. A diagnosis of angioneurotic edema was made.

The lesions cleared gradually. On January 29, five days after admission, his temperature was 100 F., and he complained of a generalized headache. The headache increased, and aches in the arms and the back, anorexia and frequency and urgency of urination appeared together with a rise of temperature to 102 F. At night he slept soundly and was incontinent of urine and feces. The following morning lethargy and generalized abdominal cramps were present, and it was noted that the deep reflexes were present and normal. That night he climbed out of bed and voided twice on the floor. On February 2, nine days after admission, his condition was unchanged; fever persisted at the same level and the results of neurologic examination were described as negative. For the first time the suspicion arose that this was a case of schistosomiasis. A stool was reported to contain no ova or parasites on February 3. A blood smear was negative

for malaria, and the differential count showed 60 per cent eosinophils. In the next several days lethargy, incontinence, generalized aches and thoracic pains persisted. On February 7 the temperature reached normal. The patient was still disoriented. The liver and the spleen could not be felt. The pupils were small, and the fundi could not be seen. There was spastic quadriplegia with pathologic reflexes, although superficial reflexes were present. The sensory examination was inconclusive. Antimony and potassium tartrate therapy (1.95 Gm. of the compound, containing 0.73 Gm. of antimony) was started February 10 and completed March 12. The patient became ambulatory on his own insistence the day after therapy was begun, and in the next four weeks there was an increase of strength and appetite with a lessening of complaints. At the completion of therapy examination showed the peripheral visual field and the fundus normal, the left patellar and ankle jerks hyperactive, the pathologic reflexes normal and the flexor muscles of the right arm and the left leg still weak. Abdominal distress, cramps in the legs and heaviness were occasionally complained of thereafter until April 28, three months after admission, when a careful detailed examination revealed normal conditions with the exception of a hyperactive Achilles tendon reflex with transient clonus.

The patient was transferred to a center for convalescents.

Summary.—Two months after exposure this man suffered from angioneurotic edema, headache, lethargy, incontinence, change in personality and spastic quadriplegia. Leukocytosis was not present on one examination, although eosinophilia was severe. Ova of S. japonicum were not demonstrated. Two fellow soldiers who had been exposed with him were in the hospital at the same time with proved schistosomiasis.

CASE 3.—A 20 year old white infantryman was admitted to a clearing station on Feb. 2, 1945, complaining of cough and fever of eight days' duration. At the clearing station it was noted that the illness started with an occasionally productive cough, followed by generalized aches.

Fever was present; it was minimal, with the temperature ranging between 99.2 and 100.4 F. by mouth. The patient was thought to have acute bronchitis. Although the cough cleared in a few days, he remained vaguely uncomfortable. Seven days after admission, while he was ambulatory, there was a sudden change in his condition. He became listless, depressed, slightly confused, uncooperative and complained of "feeling bad." The temperature was 100 F. Examination at this time revealed no explanation for the change of condition. Hysteria was considered probable, and he was transferred to the hospital, February 12. On admission the history was sketchy but of some value, and as time went on completion of the history was accomplished.

Arriving on Leyte, Oct. 24, 1944, the patient had been perfectly well until two weeks before he sought medical attention. He swam many times in the rivers of this island, his last exposure being one month before he became ill. Two weeks before he went to the clearing station, a cough developed, which persisted, accompanied with malaise and fever. There were no headaches, visual disturbance, vomiting, eruptions or paresthesia. Two days prior to admission, while in the previous installation, he lost control of his arms, was nervous and was unable to sleep. The left arm rapidly became weak in the two day period. There was no history of swimmer's itch, urticaria or diarrhea. A fellow soldier who had been swimming with him was under observation for schistosomiasis.

Family and personal histories were noncontributory.

Examination disclosed a husky white soldier, who was conscious, listless and lethargic; his response to questions was slow and blocked, and comprehenion was lacking. There was no icterus or eruption of the skin. The pupils reacted normally, and an examination of the fundi revealed nothing abnormal. External ocular movements seemed normal, but cooperation was not secured. The remainder of the examination of the head, the neck, the lungs, the heart and the abdomen gave normal results. The liver and the spleen were not palpable. The cranial nerves were normal; the left upper extremity was not moved voluntarily and was flaccid, and deep reflexes of this extremity were not obtained. The leukocyte count was 23,800, of which 80 per cent were eosinophils. The spinal fluid was clear; it was not under pressure and contained 3 lymphocytes; the globulin was not increased. The urine was normal except for a faint trace of glucose.

The patient spent a restless night and complained of an ache in the left elbow. The following morning he was less drowsy but still listless, reacted to commands slowly and had a peculiar blank stare. The left arm was unchanged; the eyes were normal, and the equivocal Babinski reflex was present bilaterally.

Fuadin therapy (45 cc. of fuadin, containing 0.38 Gm. of antimony) was started on February 14 and completed on March 2. The day after therapy was started a slight improvement in the mental status was present, and simple questions were answered more rapidly. Biceps and triceps reflexes were just present, and there was a slight increase of power in the left arm. In the next three days the patient became alert, moved his left arm voluntarily and talked freely with his fellows. It was noted that although he moved his left arm it was much weaker than the right. There was little change thereafter until the completion of treatment on March 2, when examination disclosed that he was stronger generally and that ataxia of the left hand and clumsiness of the fingers (tying pajamas) were still present. The deep reflexes of the right upper and the left lower extremity were somewhat hyperactive. Sensory examination in all modalities showed normal conditions, and muscle power was apparently normal. Ten days later examination showed that the peripheral fields of vision were normal. There were no outstanding changes thereafter. He was treated on two occasions for hookworm and ascariasis and was transferred to the convalescent section of the hospital. On April 24, eleven and a half weeks after admission, he was well except for some weakness of the left arm—"it felt paralyzed." This condition was especially noticeable when he wrote (left-handed). Examination revealed entirely normal conditions. On May 3, a stool specimen contained S. japonicum.

Summary.—Within three months after exposure this man had cough, malaise and fever, followed by monoplegia, lethargy, blocking and transient involvement of the pyramidal tract affecting the lower extremities. Three months later subjective symptoms were present. Leukocytosis with eosinophilia was observed, and numerous parasites were present in the stool. Ova of S. japonicum were not demonstrated until after convalescence had started.

CASE 4.—A 28 year old white soldier was admitted to a battalion aid station on Jan. 16, 1945, complaining of fever. His temperature was 101 F., and he was thought to have dengue. Three days later slurred speech, incontinence, a bilateral Kernig sign and a left Babinski reflex were present, and he was transferred to an evacuation hospital. Here it was noted that he was lethargic and responded only by shaking his head. On examination there was no nuchal rigidity, and the pupils were equal and regular. The deep reflexes of the upper and the lower extremities were hyperactive; the Babinski reflex, confirmatory reflexes

and ankle clonus were bilaterally present; the abdominal and cremasteric reflexes were absent, and the lower extremities were spastic but not paralyzed. A spinal tap was done; the fluid was clear, was not under increased pressure and contained 6 cells.

The patient was then transferred to a station hospital on January 25. On admission it was noted that a reliable history was unobtainable.

He had arrived in Leyte on Nov. 23, 1944. From that date until the end of November he had gone swimming many times in fresh water streams. Six weeks before admission he had generalized headaches, malaise and fever. He was very hazy in regard to events after that but did not recall "swimmer's itch," hives or cough.

The family history was noncontributory except for paternal hypertension.

Other than for "glands on the left side of the neck" as a child and pneumonia in 1940 he had been in excellent health.

Examination disclosed an acutely ill man who was conscious and answered simple questions hesitatingly and whose frequent exhalations caused fluttering of the lips. His voice was hoarse. He was cachectic and appeared twice his supposed age. Loss of weight was apparent. The left pupil was larger than the right; both reacted to light, and the left lid was slightly ptosed. External ocular movements could not be tested; there was no apparent visual disturbance or deafness. The tongue was dry. The temporal arteries were prominent. There was moderate nuchal rigidity. The heart, the lungs, the abdomen, the genitalia and the articulations were normal. There was no adenopathy. The blood pressure was 104 systolic and 88 diastolic. The right upper extremity was held in constant flexion of the elbow, and the left upper extremity was also spastic; the left lower extremity was flaccid, but some voluntary motion was present. There was a suggestion of weakness of the left seventh nerve. All deep reflexes were hyperactive, and the superficial reflexes were absent. The Babinski reflex, confirmatory reflexes and ankle clonus were present bilaterally. Sensation was intact.

The temperature ranged from 98.6 to 101.6 F. for one week. Semicoma supervened; the pupils became pinpoint in size, and incontinence continued. Three days after admission the liver was palpable 2 fingerbreadths below the costal margin and was extremely tender. Fuadin therapy was started on Jan. 29, 1945 and completed on March 5 (90 cc. of fuadin, containing 0.76 Gm. of antimony). Shortly after therapy was started, he showed signs of improvement, and voluntary movements were increased in the lower extremities. One week later (February 4) he appeared confused, withdrawn and somewhat agitated. Although cerebration was slow and insight lacking he tried to cooperate. He took an interest in his examination for the first time. There was paresis of the lower left side of the face; the left pupil was greater than the right, but both reacted normally. The left side of the palate was weak. Both upper extremities were weak, the left more than the right; the involvement of both lower extremities was less. Bilateral ankle clonus persisted, and the superficial reflexes were still absent. The liver was just palpable and extremely tender. The patient was admitted to the hospital during his fourth week of illness, February 11. He was still unable to give a coherent story. The cranial nerves were intact. Apraxia was present. Simple commands were executed promptly and well, but he had difficulty in choosing words and expressing himself; he was oriented and repeated test phrases. Reflexes were hyperactive with bilateral Babinski reflex and ankle clonus and Oppenheim and Gordon signs on the left side. The blood pressure was 90 systolic and 58 diastolic. The heart and the lungs were normal; the liver was still tender; the spleen was not palpable. In the next two weeks marked progress was made;

control of the bladder was regained, and speech was almost normal. However, simultaneous walking and response to commands were hesitant, unsteady and slow, and he was absentminded. Arthralgia of the large joints was present. The Romberg sign was not present. The fingers were more dextrous. The deep reflexes were greatly increased in the left upper and lower extremities, with associated muscular weakness. Transient left ankle clonus was present, and the superficial reflexes were still absent. Heat and cold sensation were diminished in both legs and feet. The fundi and the peripheral parts of the visual fields were normal. During the next several weeks the patient made good progress. On April 20, seven weeks after the completion of therapy, all his previous disturbances, while present, were less acute. The reflexes were unchanged; the left ankle clonus was sustained; the left upper extremity was moderately weaker than the right, and the left lower extremity was weak, with incomplete foot drop. Shortly afterward he was evacuated to the United States.

Summary.—Two months after exposure this man suffered from diarrhea, headaches, malaise, fever, confusion, aphasia, involvement of cranial nerves, semiconsciousness and paraplegia. After two months there was still residual paralysis. Leukocytosis, eosinophilia and transient roentgenographic pulmonary shadows were present. Ova of S. japonicum were not demonstrated.

CASE 5.—A 27 year old white American soldier was first admitted to another hospital on Feb. 2, 1945, complaining of weakness in walking, pains in the left arm and cough severe enough to prevent sleep. The notes made at that admission are scanty but indicate that he had bathed and swum in rivers on Leyte. One month previously he had been admitted to that hospital for a few days because of fever. The positive findings recorded at that time were mild generalized adenopathy, specifically prominent in the axilla and the groin, obvious instability and ataxia on walking. The temperature was 99.4 F., the pulse rate 80 and the respiratory rate 20. The severity of the pain in the arm required frequently repeated administration of morphine for relief. On admission the leukocyte count was 19,000, with 60 per cent eosinophils. Examination of a stool revealed no ova or parasites. The next day restlessness was disturbing, and the patient would not lie still because of pain in the left shoulder. In the morning he answered questions slowly and was drowsy. There were no signs of meningeal involvement, and the Babinski and confirmatory reflexes were not present.

On February 25 the patient was transferred to this hospital. On arrival he was mute, not responding to questions; he continuously tried to sit up in bed and then would fall to the left. There were constant choreoathetotic movements of the arms and the fingers. Restraints were required.

The following history was taken at a later date: He had been perfectly well until Jan. 8, 1945. He arrived on Leyte, Dec. 25, 1944, and bathed in the streams from that time until Jan. 1, 1945. He noted dull generalized headaches, with occasional sharp scattered head pains and eyeache on January 8; these were constant and prevented sleep. Some time later, severe aching pain began in both shoulders. He continued on duty because of an imminent important military operation. He was hospitalized three to four weeks later because of fever which had been present for an unknown period. At this time he had a cough. He was released from the hospital and was rather vague in his description of what occurred thereafter, but stated, "I must have gone out of my head and was sent to the hospital." He recalled going to the hospital and then was amnesic until seven days after admission to the second hospital. There was no history of "swimmer's itch," urticaria, abdominal pain, vomiting or diarrhea.

The family history was noncontributory. The patient had pleurisy in 1931.

On examination the temperature was 100.4 F. The patient was a dark-complexioned soldier, husky, muscular and in constant motion, rolling to the left. There were no signs of recent trauma. The pupils were equal and small and reacted sluggishly to light. The conjunctivas were clear. External ocular movements could not be tested. A technically difficult examination of the fundi revealed no abnormality. There was slight nuchal rigidity. The lungs were clear except for an occasional transient squeaking rale in the lower lobe of the left lung. The heart was normal, with a rate of 80, and the blood pressure was 130 systolic and 90 diastolic. The liver and the spleen were not palpable. He was conscious but unresponsive. Other than pupillary changes there was no sign of involvement of the cranial nerves. The deep reflexes were hyperactive in the right upper and lower extremities, with equivocal Babinski reflex and sustained ankle clonus; the deep reflexes were absent in the left upper extremity and exaggerated in the lower extremity, with pathologic reflex, and all superficial reflexes were absent. Sensory examination was not possible. A spinal tap (patient struggling) was done. Ten cubic centimeters of crystal clear fluid was obtained, having an initial pressure of 240 mm. of water. There were 22 cells per cubic millimeter (differential count not done); a test for globulin was negative; the glucose content was 87 mg. per hundred cubic centimeters. The leukocyte count on the blood was 16,700, with 78 per cent eosinophils, 10 per cent neutrophils and 12 per cent lymphocytes.

The patient was given sedative treatment, and fuadin therapy was started on February 25 and completed on March 20 (60 cc. of fuadin, containing 0.51 Gm. of antimony). For the next several days there was no apparent change; a low grade fever, with the temperature elevated to 100.4 F., continued, and incontinence persisted. One week later, March 1, he was less confused and spoke monosyllabically. Voiding was frequently voluntary, with periods of retention. When he was urged, he would move his left arm, but otherwise it was not moved. Restlessness prevailed at night. In the following week progress was evident. Examination of the peripheral fields and the fundi during this period revealed no abnormalities. Two weeks later, March 16, he was rational and oriented; speech was slurred; he was unable to repeat test phrases and was extremely clumsy in lighting cigarets; fine movements of the left hand were difficult. The cranial nerves were intact. The left upper extremity was weak, and its reflexes were more hyperactive than those of the right; the reflexes of the right lower extremity were increased, but those of the left were absent. There were no pathologic reflexes except for a transient left clonus; the superficial reflexes were normal and the sensory examination revealed normal conditions. Walking was accomplished with slight difficulty, owing to weakness rather than ataxia; a gain in weight of 10 pounds (4.5 Kg.) was noted on March 27. Four weeks later progress continued, but there was still complaint of weakness of both legs. Although the patient thought that his memory was normal, he was still unable to repeat test phrases. Finer movements were more skilfully performed. There was slight ataxia of the feet. The reflexes of the lower extremities were unchanged; on the left side Babinski's reflex and Oppenheim's sign were still present. Muscular strength was now normal. A few days later, April 3, he was asymptomatic and began convalescent training (consisting of gradually increasing exercise under supervision). When he had his final examination, April 29, he felt weak and his left arm still troubled him occasionally. The deep reflexes in the left arm and leg were hyperactive, but pathologic reflexes were no longer present. The head, the neck, the heart, the lungs, the abdomen and the genitalia were normal. The liver

and the spleen were not palpable, and muscular power was normal. He was evacuated to the United States.

Summary.—About six weeks after exposure this man had cough, fever, malaise, scattered pains, amnesia, aphasia, choreoathetotic movements, incontinence and triplegia. Subjective symptoms and neurologic findings were still present three months after the onset of illness. Leukocytosis and striking eosinophilia were present. Ova of S. japonicum were not found.

Case 6.—A 23 year old white soldier was first seen at a clearing station on Jan. 30, 1945, complaining of exhaustion. It was noted there that he was vague, uncooperative, disoriented and incontinent. He was transferred to a hospital on February 1. On arrival he was comatose, and a history could not be obtained. Examination disclosed a well developed, well nourished white soldier in coma. He had a pulse rate of 100, a blood pressure of 118 systolic and 70 diastolic, and a respiratory rate of 18. The general attitude appeared at first to be that of catatonia in flexion, but further examination disclosed that there were spasticity and rigidity in flexion, involving both extremities, more marked on the left side. The hands were tightly clenched, with flexion at the wrists and the elbows, the arms being drawn inward so that the fingers rested on the chest at about the manubrium; the legs disclosed only moderate spasticity on flexion, the left more than the right. Movements of the head were resisted in all directions. There was no syndrome of decerebrate or decorticate rigidity, and the optic disks appeared normal. The third, the fourth and the sixth cranial nerves showed inconstant deviation, apparently due to supranuclear involvement. The eyes wandered coordinately at times. There was definite masking of the facies but no definite paresis. The deep reflexes were hyperactive, more so on the left side, with so much spasticity and rigidity that the amplitude of response was limited, and all superficial reflexes were absent. There was too much spasticity in flexion to elicit a Hoffmann sign. The Babinski reflex was bilaterally positive, more so on the left side, and the Chaddock sign was positive on the left side but questionable on the right. The leukocyte count was 16,400, with a differential count of 62 per cent neutrophils, 28 per cent lymphocytes and 10 per cent eosinophils. It was thought that diffuse encephalitis, with probable involvement of the deeper structures, basal ganglions and pyramidal tract was present. The next day, February 2, a blood smear was negative for malaria. The leukocyte count was 23,200, with 45 per cent eosinophils. Clear spinal fluid was obtained, which was under pressure of 16 mm. of mercury, and did not contain cells. The urine was normal. A roentgenogram of the skull revealed nothing. For the next week, February 2 to February 6, there was no evident change. The temperature was elevated to between 102 and 103 F. During this time penicillin, 25,000 units, was given every three hours. On February 3, examination of a stool showed no ova. The total leukocyte count was 19,100, with 40 per cent eosinophils. A second spinal tap showed clear fluid under pressure of 14 mm. of mercury, containing 2 to 3 cells per cubic millimeter.

On the basis of the clinical and the blood picture a tentative diagnosis of schistosomiasis was made, and a course of fuadin was started on February 10 and completed on March 16 (80 cc. of fuadin, containing 0.68 Gm. of antimony). The administration of penicillin was continued for ten days. The patient improved slowly, and the temperature fell by lysis. During this time 3 men from his unit were found to have stools containing S. japonicum. They said that they had been swimming with the patient in Leyte one and a half months ago. On February 12, a specimen of stool contained ova of S. japonicum. By February 14 (four days after the onset of the fuadin therapy) the patient had made remarkable progress.

He was conscious and responded to simple questions in monosyllables or in two or three words. He opened his mouth and protruded his tongue, although slowly and with apparent difficulty. Some comprehension of vision was apparent, but the sensorium was not clear enough or responsive enough for the determination of homonymous defects of visual fields. The spasticity in flexion was still present in the upper extremities, more on the left, so much so that he had excoriated the skin over the manubrial and adjacent areas. Bilateral ankle clonus, Babinski's reflex and Chaddock's sign were present; the masklike facies was persistent, and a mild form of Horner's syndrome was suggested. It was now thought that diffuse encephalitis involving the right hemisphere more than the left and due to S. japonicum was present. On February 25 he was transferred to the hospital where this collection of cases was made. On admission he was disoriented. The history of his illness was obtained weeks later.

He arrived in Leyte, Nov. 23, 1944. During the first week of December he frequently swam in the fresh water streams of this island. About one month later, early in January 1945, chills developed, with pains in the chest—aching in character—and a nonproductive cough (like a cigaret cough). Then pains developed in both upper quadrants of the abdomen, which "came and went," and about the middle of January an urticarial eruption developed; soon fever, frontal headaches and generalized abdominal pains recurred, and he was confined to his quarters. His condition suddenly became worse, and medical attention was sought. He was completely amnesic from then on until he was treated in this hospital.

His family and personal histories were noncontributory.

On admission he was much more agitated than the previous note indicated. He constantly and aimlessly tried to get out of bed; he would crawl to a sitting position, his entire trunk would twist to the right, and he would fall. This happened again and again. Both upper extremities were continuously in athetotic motion. His speech was slow and monosyllabic; the pupils were normal; the mouth could not be examined, and the neck was held stiffly but in rare moments appeared only slightly resistive. There was no adenopathy. The heart and the lungs were normal; the abdomen was voluntarily rigid, so that palpation was valueless, but hepatic tenderness was not present, and neither the liver nor the spleen when percussed seemed enlarged. There was spasticity of all extremities; superficial reflexes were not obtained, there was hyperreflexia throughout, and Babinski's reflex and clonus were bilaterally present. About two weeks after fuadin therapy was begun, four days after admission on March 1, he was apparently clear mentally; ataxia was less, and he understood the use of the urinal. His appetite was ravenous. There was definite improvement; speech now consisted of several words; euphoria was evident, a fatuous grin alternating with a masklike facies. The dystonic movements to the right were less; his reaction to a command was slow, but he answered simple questions slowly, rationally and coherently, in a monotonous voice. He was unable to write; the motions were wasteful, irregular and jerky. Incontinence was no longer present. A nontender liver was palpable 2 fingerbreadths below the costal margin; the cranial nerves were intact, and muscular strength approached normal. All deep reflexes were markedly hyperactive, more so on the right. There was bilateral ankle clonus with a normal plantar reflex; the abdominal reflexes were equal, and the left cremasteric reflex was absent. There were no sensory changes, and he was ataxic only with his eyes closed. There was bilateral apraxia as well as adiadokokinesis. At the conclusion of therapy (five weeks), three weeks after admission to this hospital, he fed himself and carried on long conversations with his neighbors; attendants were

no longer necessary. The peripheral parts of the fields of vision and the fundi were normal, but ataxia and bilateral clonus were still present. In the next few days he had mild discomfort from an infection of the upper part of the respiratory tract. On March 29, two weeks later, he had made further progress. Insight was present; speech was clear. He was mildly agitated and was unable to read because of forgetfulness. There was finger incoordination as well as bilateral intention tremor; ataxia was greater on the left side than on the right; there was no discernible weakness of the spastic lower extremities, and Romberg's sign was not present. He made slow but steady progress, particularly in coordinated movements. On April 24, mild coryza, nausea, anorexia and epigastric soreness developed. Two days later he became icteric and was returned to bed with a diagnosis of infectious hepatitis, then prevalent in Leyte.

Summary.—One to two months after exposure this man suffered from pain in his chest, cough, eruption, fever, headache, amnesia, extrapyramidal tract signs, incontinence and quadriplegia. Two and a half months later residua were still present. Leukocytosis and severe eosinophilia were present. Ova of S. japonicum were demonstrated.

CASE 7.—A 29 year old white soldier surveyor was admitted to a previous hospital installation, Jan. 15, 1945, for hemorrhoidectomy, which was done the following day. On January 21, fever, symptoms of bronchopneumonia, disorientation and confusion were present, and the patient showed motor weakness of the left hand. The next day the leukocyte count was 20,000, with eosinophils 36 per cent, neutrophils 44 per cent and lymphocytes 20 per cent. The urine was normal, and a roentgenogram showed that the chest was normal. The spinal fluid was crystal clear; the leukocyte count was 2, and the Pandy test was negative. Ova of S. japonicum were found in the stool. As a result of these findings the patient was transferred, January 24, to the hospital where this collection of cases was made, with a diagnosis of schistosomiasis with cerebral involvement. On admission the patient was obviously confused and complained of difficulty in thinking and concentration.

He had arrived on Leyte, Oct. 24, 1944. He bathed frequently in local streams and had also waded frequently through rice paddies from Nov. 15, 1944 to Jan. 1, 1945. About five days before he underwent hemorrhoidectomy he had epigastric pain and soreness, which were worse at night and spread to the lower part of his chest bilaterally along the lower ribs; simultaneously hives broke out, which cleared before his admission to the hospital. He had never noticed "swimmer's itch," diarrhea, abdominal pain or anorexia prior to the aforementioned developments. After the operation he became acutely ill, with a temperature of 103 to 104 F., severe pain in his chest, cough, generalized urticaria, mental confusion and delirium. The fever lasted a few days. After subsidence of the acute phase he noted persistent increasing weakness, insomnia, difficulty in thinking and orientation, confusion and poor memory, numbness in the left arm and in the legs and, later, weakness of the left arm. He had been a printer until two years before admission.

On examination his temperature was 102 F.; the pulse rate was 88, and the respiratory rate was 20. The patient was small, weighing 140 pounds (63.5 Kg.), chronically ill and pale, lying quietly in bed. He was confused, apprehensive and oriented to place only. The head, the neck, the heart, the lungs, the abdomen and the genitalia were normal; the liver and the spleen were not palpable. The blood pressure was 110 systolic and 70 diastolic. There was no adenopathy. The cranial nerves were intact. There was extreme weakness of the left upper

extremity, with hyperreflexia. The deep reflexes of the right upper extremity were normal; the reflexes were absent in the left and exaggerated in the right lower extremity. There was bilateral ankle clonus; superficial reflexes were not present. Sensation was normal.

The condition did not change during the next several days. The patient became jumpy and agitated at night; he repeatedly removed his pajamas and then put them on again. He was aphasic in the use of common articles, such as knife, spoon, fork and shaving equipment. Antimony and potassium tartrate therapy was begun on February 1 and completed on March 3 (1.95 Gm. of compound containing 0.73 Gm. of antimony). The day after the start of therapy, vertigo and nystagmus to the left appeared, which lasted three days. He had difficulty in remembering names and in smoking cigarets, and he was unable to write. He was cooperative, alert and coherent, but his speech was slurred. He read and comprehended print. Other than ataxia, adiadokokenesis and slow associated movements on the left side there were no new changes. About five days after the onset of therapy, February 6, he felt better than he had in many weeks; he was more alert and was allowed to walk. For the next two weeks there was a steady return to normal. Transient abdominal distress was present in the left lower quadrant. He was irritable at night. The spleen was palpable for the first time just below the costal margin, and it was noted that although pyramidal tract signs persisted, coordination was better. On March 7, one month after therapy was begun, when he was questioned closely, he admitted that his unsteadiness in walking increased in the dark and that when he concentrated he could give an outward appearance of steadiness but actually felt unsteady. Weakness was less, and memory was excellent. Gain in weight was apparent. The Romberg sign was positive and his gait was slightly ataxic. Involvement of the extremities and ankle clonus were still present, and abdominal reflexes were obtained for the first time. There were adiadokokinesia and apraxia on the left. Fundi and peripheral parts of the visual fields were normal. Ten days later he was able to walk to the mess hall, a distance of 200 yards (182 M.). There was a gradual increase of strength in the ensuing weeks. On the final examination, April 29, he stated that he was unable to concentrate, that his memory was extremely poor (contrary to his previous report) and that he was unable to do automatic acts, such as walking and answering questions simultaneously when addressed—it was necessary for him to stop walking before he spoke or he would fumble his steps. He had gained approximately 10 pounds (4 Kg.). The liver was firm, irregular and palpable 2 fingerbreadths below the costal margin; the spleen was not palpable, and writing was normal. The deep reflexes were still exaggerated, and bilateral suprapatellar clonus had appeared in addition to the ankle clonus. He would constantly overshoot to the left in bringing his finger to the nose. Romberg's sign was now not present; adiadokokinesis and apraxia were still present, and the left upper extremity was weaker than the right.

Summary.—After a two and a half month period of exposure this man suffered from fever, cough, confusion, abdominal pain, urticaria, paresthesias, aphasia and paresis of the left upper extremity and both lower extremities. Residua were present three months after the onset of illness. Leukocytosis and eosinophilia were present. Ova of S. japonicum were demonstrated.

SYMPTOMS

Suspicion of the presence of schistosomiasis should be immediately aroused when there is a history of geographic exposure. The disease is

endemic in the Far East, having been observed in scattered areas of China, particularly the Yangtse Valley, in scattered areas of Japan and in localized areas of the southern Philippine Islands especially Leyte. If there is a history of residence in these areas, careful inquiry should establish specific exposure to contaminated water by drinking, bathing, washing or wading in fresh water streams or rice paddies. The relationship of exposure to the onset of symptoms is important, since in this group acute manifestations began within three months after contact with contaminated water.

A few weeks after contact with contaminated water, malaise, generalized aches, fever, urticaria-like eruption, angioneurotic edema, cough, pain in the chest, abdominal pain and diarrhea may occur. Frequently dengue, malaria, bronchitis, bronchopneumonia or dysentery is diagnosed at this stage even by observers who are cognizant of the disease.

Fever, malaise and generalized aches are not especially characteristic and may be so mild that medical attention is not obtained. Symptoms of involvement of the respiratory tract may appear soon after the fever. First among these is a nonproductive cough; rarely some mucoid material is produced after a paroxysm of coughing. Vague pains and aches occur in the chest which are not related to the cough or the respiration. These pains are mild and fleeting, and the patient may not mention them unless directly interrogated. Hemoptysis is most unusual. Urticarial eruptions, which may appear simultaneously with or follow the fever and the symptoms of involvement of the respiratory tracts, are characterized by their occurrence in a person who does not have an allergic background. The urticaria is generally of the giant type, transient, recurring for several days. Diarrhea is not significant and is difficult to evaluate, since gastrointestinal symptoms are commonly seen in many diseases of this region. Abdominal pain, though important, is rarely severe; while it is frequently generalized, it is more often located in the epigastrium and the right upper quadrant and is described as an "ache" and occasionally as "cramps."

PHYSICAL EXAMINATION

Few specific and characteristic abnormalities are disclosed in physical examination. Fever is variable in degree and duration, but when severe it may be accompanied with late afternoon sweats and chills. Severe cough when present is inadequately explained by the examination of the lungs; rarely, scattered rales and rhonchi are heard, but as a rule the examination reveals nothing pertinent. The liver is tender and palpable. Tenderness is best brought out by indirect heavy percussion, and palpation in the usual manner may not detect it. The eruptions encountered are definitely urticarial; large areas of the skin may be involved, and angioneurotic edema of the lips, the cheeks, the hands and the feet is not unusual.

TABLE 1.—*Laboratory Data in Seven Cases*

Date	Hemoglobin, %	Blood Count: Red Cells	Blood Count: White Cells	Blood Count: Eosinophils, %	Urine	Malarial Parasites in Blood Smear	Erythrocyte Sedimentation Rate, Mm. in 1 Hr.	Spinal Fluid	Kahn Test of Blood	Ova or Parasites in Stools	Roentgen Findings
				Case 1. Exposure: 10/20/44 to 12/31/44. Hospitalized: 1/9/45							
1/10/45	..	.....	.....	..	.....	.....	..	Normal pressure; 12 cells			
1/11/45	..	.....	27,400	38	Normal	None					
1/13/45	..	.....	39,100	46							
1/14/45	..	.....	25,000	54	.....	.....	..	Normal pressure; 3 cells Pandy test negative			
1/17/45	..	.....	.....	..	.....	.....	..	.....	.....	Hookworm, S. japonicum	
1/17/45	(Treatment with fuadin started)										
1/23/45	..	.....	28,400	61	.....	.....	..	.....	.....	Hookworm, S. japonicum	
1/29/45	..	.....	.....	..	.....	.....	36	.....	.....	Hookworm, S. japonicum	
1/31/45	..	.....	25,000	27	.....	.....	..	.....	.....	None	
2/ 2/45	..	.....	.....	..	.....	.....	..	.....	.....	None	
2/ 4/45	(Treatment with fuadin completed)										
2/17/45	..	.....	.....	..	.....	.....	1				
2/10/45	..	.....	21,000	55	.....	.....	..	.....	.....	None	
2/12/45	..	.....	18,500	39	.....	.....	..	.....	.....	None	
2/17/45	..	.....	18,600	40	.....	.....	..	.....	.....	Hookworm	Heart and lungs normal
2/26/45	..	.....	.....	..	.....	.....	..	.....	.....	None in many specimens elsewhere	
				Case 2. Exposure: 12/20/44 to 12/25/44. Hospitalized: 1/24/45							
2/ 8/45	..	.....	.....	60	.....	None	..	.....	.....	None in 15 specimens	
2/10/45	(Treatment with antimony and potassium tartrate started)										
2/13/45	..	.....	.....	..	.....	.....	..	Normal pressure; cells 0; globulin 0; Kahn test neg.; colloidal gold curve 000 000 000 0	Neg.		

3/ 5/45	..	.....	.....	..	.....	.....	..	.....	.....	.....	Hazy, indefinite mottling in both lung fields
3/ 8/45	..	.....	.....	..	.....	None	8				
3/ 9/45	..	.....	.....	..	.....	.....	..	.....	.....	.....	Lung fields clear
3/12/45	..	.....	7,400	27	Normal	None					
3/12/45	(Treatment with antimony and potassium tartrate completed)										
4/ 2/45	100	5,000,000	.....	..	.....	.....					
					Case 3. Exposure: 10/24/44 to 12/31/44. Hospitalized: 2/1/45						
2/ 9/45	..	.....	.....	70	.....	None	..	.....	.....	32, specimens: hookworm, A. lumbricoides cysts E. histolytica, sporadically present	
2/12/45	..	.....	24,600	61							
2/13/45	95	4,600,000	.....	..	Glucose +	.....	..	Normal pressure; 3 lymphocytes; glucose 0; globulin 0; Wassermann test neg.; colloidal gold curve 000 000 000 0			
2/14/45	85	.....	23,800	52	Normal						
2/14/45	(Treatment with fuadin started)										
2/16/45	80	3,500,000	.....	82	.....	.....	..	.....	.....	.....	Heart and lungs normal
3/ 2/45	(Treatment with fuadin completed)										
3/12/45	..	.....	.....	..	.....	.....	..	.....	.....	S. japonicum	Skull normal
4/ 2/45	..	4,500,000	7,400	10	.....	.....	15				
5/ 3/45	..	.....	.....	..	.....	.....	..	.....	.....	.....	
					Case 4. Exposure: 11/23/44 to 11/30/44. Hospitalized: 1/16/45						
1/16/45	..	.....	.....	..	.....	.....	..	Normal pressure; 6 cells	.....	None in 20 specimens	
1/27/45	..	4,900,000	21,200	17	Normal	None	8				
1/29/45	(Treatment with fuadin started)										
1/30/45	..	.....	.....	..	.....	.....	..	Normal pressure; 13 cells (lymphocytes 10, polymorphonuclears 3); globulin 0; glucose 65 mg. per 100 cc.; Kahn test neg.; colloidal gold curve 000 000 000 0; sterile			
2/ 2/45	90	5,100,000	12,600	29							
2/ 5/45	90	5,200,000	15,900	41	Normal						

TABLE 1.—*Laboratory Data in Seven Cases—Continued*

Date	Hemoglobin, %	Blood Count: Red Cells	Blood Count: White Cells	Blood Count: Eosinophils, %	Urine	Malarial Parasites in Blood Smear	Erythrocyte Sedimentation Rate, Mm. in 1 Hr.	Spinal Fluid	Kahn Test of Blood	Ova or Parasites in Stools	Roentgen Findings
Case 4. Exposure 11/23/44 to 11/30/44. Hospitalized: 1/16/45—Continued											
2/ 6/45	90	5,200,000									
2/15/45	..	.....	.....	..	.....	.....	..	.....	.....	.....	Indefinite hazy mottling of lungs
2/25/45	90	4,900,000	9,800	16							
3/ 5/45	(Treatment with fuadin completed)										
3/ 6/45	..	.....	.....	..	.....	.....	..	.....	.....	.....	Shadows unchanged; skull normal
3/ 8/45	90	4,000,000	9,500	11	Normal	.....	11	.....	Neg.		
3/10/45	..	.....	.....	..	Normal	.....	..	.....	.....	.....	Upper lung fields clear
3/22/45	..	.....	.....	..	Normal	.....	..	.....	.....	.....	Lungs clear except for hazy mottling at left base
3/26/45	..	.....	13,700	6							
4/23/45	90	.....	16,300	16							
Case 5. Exposure: 12/25/44 to 1/1/45. Hospitalized: 2/2/45											
2/ 2/45	..	.....	19,000	60	.....	None	..	.....	.....	None in 20 specimens	
2/23/45	..	.....	19,000	60	.....	None					
2/25/45	..	.....	16,700	78	Normal	None	..	Pressure (struggling) 240 mm. water; 22 cells glucose 87 mg. per 100 cc.; globulin 0			
2/25/45	(Treatment with fuadin started)										
3/ 2/45	..	.....	.....	..	.....	.....	..	.....	.....	.....	Heart and lungs normal
3/ 3/45	95	4,500,000									
3/ 7/45	..	.....	.....	..	.....	.....	..	.....	.....	.....	Skull normal
3/ 9/45	..	.....	.....	..	.....	.....	..	.....	Pos.		
3/15/45	..	.....	.....	..	.....	.....	..	.....	Neg.		

3/19/45	95	5,100,000	13,400	44	.....	None					
3/20/45	(Treatment with fuadin completed)										
3/27/45	..	.....	15,900	27	.....	None					
4/14/45	..	.....	10,900	18	.....	None	7				
					Case 6. Exposure: 12/1/44 to 12/7/45. Hospitalized: 1/30/45						
2/ 1/45	..	.....	16,400	10							
2/ 2/45	..	.....	23,200	45	Normal	.....	..	Clear; pressure 16 mm. Hg; cells 0	.....	.....	Skull normal
2/ 3/45	..	.....	19,100	40	.....	None	..	.....	.....	None	
2/ 6/45	90	4,000,000	19,000	40	Normal						
2/ 8/45	..	.....	.....	45	.....	.....	..	Clear; pressure 14 mm. Hg; cells 5	.....	.....	Lungs clear; heart normal
2/10/45	(Treatment with fuadin started)										
2/12/45	..	.....	.....	..	.....	.....	..	.....	.....	S. japonicum	
2/14/45	..	.....	17,500	30	Normal	None	..	.....	.....	Repeated specimens thereafter negative (15-20)	
2/27/45	..	5,400,000	12,600	20	.....	None					
3/ 1/45	..	.....	.....	..	.....	.....	1				
3/13/45	..	.....	8,800	12	.....	None					
3/14/45	..	.....	6,300	3	.....	None					
3/16/45	(Treatment with fuadin completed)										
3/27/45	..	.....	10,600	0	.....	.....					
4/25/45	90	4,500,000	10,400	6	Normal	None					
					Case 7. Exposure: 11/15/44 to 1/1/45. Hospitalized: 1/15/45						
1/ 9/45	..	.....	.....	..	.....	.....	..	.....	.....	.....	Chest normal
1/21/45	..	.....	.....	..	.....	.....	..	.....	.....	.....	Chest normal
1/22/45	..	2,200,000	20,000	36	Normal	None	..	Clear; cells 2; Pandy test negative	.....	S. japonicum	Chest normal
2/ 1/45	(Treatment with antimony and potassium tartrate started)										
3/ 3/45	..	.....	.....	..	Normal	.....	3	Clear; cells 2; Pandy test negative colloidal gold curve 111 110 000 0	Neg.	Thereafter none in 15 to 20 specimens	
3/ 3/45	(Treatment with antimony and potassium tartrate completed)										
3/ 9/45	90	3,300,000	10,000	14							
3/11/45	..	.....	.....	..	.....	.....	..	.....	.....	.....	Skull normal
3/18/45	95	4,600,000									
3/26/45	..	.....	7,900	6	.....	None					
3/26/45	..	.....	9,700	6	.....	None					
4/29/45	..	.....	7,300	10	.....	None					

TABLE 2.—*Summary of Case Reports*

Case	Landed on Leyte	Exposure	Hospitalized	Prodromal Symptoms	Time Before Cerebral Manifestations	Cerebral Manifestations	Blood Count on Admission		Ova or Parasites in Stool
							White Cells	Eosinophils, %	
1	10/20/44	Oct.-Dec.	1/ 9/45	"Fever"	3 weeks	Confusion, disorientation, involvement of cranial nerves, quadriplegia, normal sensation	27,400	38	S. japonicum, hookworm
2	11/15/44	12/20/44 to 12/25/44	1/24/45	Cough, weakness, anorexia, aches, angioneurotic edema	2 weeks	Headache, lethargy, change in personality, incontinence, quadriplegia, normal sensation	?	60	None
3	10/24/44	Oct.-Dec.	2/ 1/45	Cough, malaise, fever, "acute bronchitis"	3 weeks	Confusion, monoplegia, lethargy, transient spastic paraplegia, normal sensation	24,600	61	Hookworm, A. lumbricoides E. histolytica, S. japonicum
4	11/23/44	11/23/44 to 11/30/44	1/16/45	Headaches, malaise, fever, diarrhea, "dengue"	2 weeks	Confusion, aphasia, involvement of cranial nerves, quadriplegia, questionable sensory disturbance	21,200	17	None
5	12/25/44	12/25/44 to 1/1/45	2/ 2/45	Fever, headache, cough	3-4 weeks	Amnesia, aplasia, choreoathetotic movements, incontinence, triplegia, normal sensation	19,000	60	None
6	11/23/44	12/1/44 to 12/7/44	1/30/45	Chills, pain in chest, productive cough, rash, headache, abdominal pain	3-4 weeks	Headache, amnesia, extrapyramidal tract signs, incontinence, quadriplegia, normal sensation	16,500	10	S. japonicum
7	10/24/44	11/15/44 to 1/1/45	1/15/45 for operation	Epigastric pain, hives, pain in chest	11 days	Insomnia, confusion, aphasia, triplegia, normal sensation	20,000	35	S. japonicum

The patients with cerebral involvement presented these characteristics of schistosomiasis in addition to the signs and symptoms resulting from the specific localization of ova: All patients were hospitalized because of the severity of symptoms within thirty-nine to a hundred days from the day of their first possible exposure (eighty-one, seventy, one hundred, fifty-four, thirty-nine, sixty-eight and eighty-three days). All had prodromal symptoms, which varied in severity and were not identical in all patients. In order of frequency the symptoms were as follows: fever, 4 patients; cough, 4 patients; weakness and malaise, 3 patients; urticarial eruption, 3 patients; headache, 3 patients; abdominal pain, 2 patients; pain in the chest, chill and diarrhea, 1 patient, respectively. Symptoms were almost always multiple in each patient. In every instance there was a lucid interval of eleven to twenty-eight days between these symptoms and the onset of neurologic disturbances. Usually the change from the prodromal to the cerebral phase was insidious, but occasionally it was abrupt.

Aphasia, amnesia, blocking, confusion, disorientation, defective memory and coma were outstanding. Spasticity, occasionally early flaccidity changing to spasticity, rigidity, hyperreflexia, pathologic reflexes and loss of superficial reflexes were common to all. In cases 1, 2, 4, 5 and 7 transient disturbances of the third, the fourth and the sixth cranial nerves were present, and in cases 6 and 7 there was questionable involvement of the facial nerve. Although motor paralysis was characteristic and involved one or more limbs, a lower motor neuron lesion did not occur in any of the patients. Sensation was not affected in any case, with the possible exception of case 4.

LABORATORY FINDINGS

The laboratory findings of schistosomiasis will be discussed both generally and specifically in relation to the neurologic disturbances.

During the period when the patients were under my observation, the first four to six months of the disease, the hemoglobin content of the blood and the erythrocyte count did not seem affected. Rarely a mild to moderate decrease of both the hemoglobin value and the red blood cell count was seen, for which another cause was generally present (malaria, malnutrition, multiple parasites). The anemia responded equally well to the administration of iron and to the therapy of the associated complication. Neither fuadin nor antimony and potassium tartrate exerted an effect on the blood count, and at the end of therapy both the hemoglobin and the erythrocytes were within the normal range.

The total leukocyte count and the eosinophil percentage were always elevated. The leukocyte count varied between 10,000 and 50,000; the eosinophil percentage also varied and within the first four months of exposure reached 40 or higher. A finding considered characteristic was

the progressive increase of eosinophilia within the first two weeks of hospitalization (cases 1, 4, 5 and 6). The neutrophil and lymphocyte percentages were not significant. Platelet determinations were not made. The significance of change in the sedimentation rate was not clear; the rate was moderately elevated in only half the cases and was generally normal at the conclusion of therapy. Frequently (incidence not determined) the roentgenogram of the chest showed changes. These consisted of soft, indefinite, hazy mottled shadows symmetrically distributed throughout both pulmonary fields, closely simulating the lesions of miliary tuberculosis but differing slightly in that they were larger, less profuse and not so sharply demarcated. At times bronchopneumonia was present, the lesions being restricted to the lower lobes. The changes lasted from two to four weeks. The effect of therapy on the disappearance of shadows could not be evaluated, as all patients whose disease was diagnosed were treated and there were no controls.

According to Johnson and Berry,[5] proctoscopic examination in 67 per cent of 63 cases showed characteristic yellow tubercles containing ova. Occasionally these were seen before ova were demonstrated in the stool. This has also been my experience, although tubercles were not seen in the patients whose stool contained no ova.

The stool was examined by many technics; the concentration method was thought to give the highest yield of positive results. While the presence of ova establishes the diagnosis, they may be extremely difficult to find, as the following history obtained from the surgical service illustrates.

A Filipino guerilla aged 24 was operated on because of a gunshot wound of the abdomen. The liver and the spleen were not large. The sigmoid flexure and the bladder were perforated in several places, and portions of the epiploic appendixes were lying free in the abdominal cavity. These when studied histologically revealed encysted ova of S. japonicum and portions of the adult worm. Stools were obtained through a colostomy wound twice daily for two days and then daily for eight days before ova were recovered from the twelfth stool. During this time hookworm ova were frequently found.

In addition to the results of the previously described laboratory procedures, those of 11 spinal fluid determinations are available in the reported cases. With the exception of a questionable elevation of the cell count in 3 cases, all results were within normal limits. The spinal fluid pressure was normal in 5 patients and elevated in 2 struggling patients. The cell count ranged from 6 to 22, including both lymphocytes and leukocytes, and was below 6 in eight specimens. The globulin was within normal limits in 4 cases. Quantitative determinations of glucose on two occasions gave 65 and 87 mg. per hundred cubic centimeters.

5. Berry, M. G., and Johnson, A. S., Jr.: Schistosomiasis, to be published.

DIAGNOSIS

When hundreds of cases appeared, it became evident that the clinical syndrome was so clearcut as to permit diagnosis in the absence of a stool containing ova. Although it was realized that a nonconfirmed clinical diagnosis was not a preferable procedure, the importance of starting therapy in an early stage of the infection outweighed the possible harm resulting from the occasional diagnostic error. As time went on justification for this point of view resulted when ova were recovered either during or long after therapy in many patients treated because of a clinical diagnosis and in the absence of rectal tubercles or characteristic ova. Case 3 is a typical example. Here a diagnosis was made clinically, and therapy was instituted. Although numerous examinations (thirty-two) of the stool had revealed no ova during three months' observation, ova were finally encountered shortly before the patients' discharge, and thus the diagnosis was confirmed. It was considered that cases 2, 4 and 5 fell into this category, and they therefore were included in this series.

Schistosomiasis can be suspected when, after the patient has been exposed to the parasite, the following appear: urticarial eruption (in a previously nonallergic subject), pulmonary symptoms, vague gastrointestinal aches, a leukocyte count over 15,000 and an eosinophil count which either exceeds 40 per cent or is shown to rise to that level by serial counts within a short period. Cerebral involvement is indicated when the neurologic signs and symptoms described appear.

When cases occur in epidemic proportion, making a diagnosis is relatively easy. In isolated instances, however, schistosomiasis with cerebral complications may be mistaken for any generalized disease in which there are cerebral involvement and severe eosinophilia.

The conditions from which schistosomiasis must be distinguished can be divided into three groups: (1) other parasitic infections: Ascaris lumbricoides, Ancylostoma or hookworm, Strongyloides stercoralis, Trichinella spiralis, Filaria; (2) neurologic disease in association with other parasitic infections, such as epidemic encephalitis and hookworm; (3) other diseases, such as allergic disorders, periarteritis nodosa, Hodgkin's disease of the skin, Loeffler's syndrome and myelogenous leukemia.

Acute hyperinfection with A. lumbricoides, hookworm or S. stercoralis may produce urticaria and pulmonary, gastrointestinal and cerebral symptoms, with severe eosinophilia, and, conceivably, at an early stage may not be distinguishable from the disease produced by S. japonicum. This difficulty of differentiation must be extremely rare and more applicable to children. During the period when schistosomiasis was rampant the hospital cared for 105 patients with A. lumbricoides, 276 with hookworm and 31 with S. stercorales, these patients presenting both single and multiple infections. The great majority of these infec-

tions were necessarily acute and of short duration. The symptoms were mild and not to be compared with those seen in the patients with schistosomiasis. Minor gastrointestinal complaints, abdominal discomfort, diarrhea and inconstant moderate eosinophilia (the count being rarely above 30 per cent) were common to the group. In only 1 patient was atypical pneumonitis encountered which might have resulted from infection with A. lumbricoides. A few cases of severe hookworm infection occurred among medical personnel at another hospital on Leyte. The outstanding features of this syndrome were fever, diarrhea, severe ulcer-like pain that was increased at night, was not relieved by an ulcer regimen and required morphine, acute anemia and marked eosinophilia. The character of the pain and the severe anemia distinguished ancylostomiasis from schistosomiasis. Severe strongyloidiasis is accompanied with severe watery diarrhea, abdominal pain and loss of weight. Ova of A. lumbricoides and hookworm and motile larvae of S. stercoralis are readily found in the stool, although occasionally they may be difficult to recover. If the cause of severe cerebral involvement is still in doubt and parasitic invasion is presumed, therapeutic trial may be most helpful. Migrating larvae will not be affected whereas there will be a definite response in schistosomiasis.

In recent years attention has been called to the association of severe eosinophilia and filariasis. Reports have appeared from widely scattered regions in the tropics, so that the syndrome due to this infection must be considered in a discussion of schistosomiasis. It is characterized by generalized lymphadenopathy, hard splenomegaly, protracted nocturnal asthma and occasionally acute nephritis.

Trichinosis may resemble schistosomiasis. The history of pork consumption, the severe muscular aches and tenderness, especially of the gastrocnemius and deltoid muscles, the conjunctival hemorrhages, the conjunctival and scleral edema, the results of a biopsy of muscle, and the negative results of examination of the stool and of proctoscopic examination should distinguish the two.

Neurologic disease in the presence of parasitic infection, excluding encephalitis, furnishes little difficulty in diagnosis. The negative results of examinations of spinal fluid in my cases are in sharp contrast with the increase of spinal fluid pressure and of cell count, globulin and glucose seen in cases of encephalitis. The tender, slightly enlarged liver, the more pronounced eosinophilia and the greater frequency of urticarial eruption in cases of schistosomiasis also aid in differentiation.

In the presence of allergic disorders the familial and personal backgrounds are helpful. Frequently a history of a similar occurrence is obtained. The chronologic order of symptoms following exposure is lacking; fever and a tender liver are not common, and eosinophilia is less severe.

The remaining group of diseases can be distinguished from schistosomiasis by a careful study of the history, particularly that of exposure followed by the typical progression of symptoms; cardiac and renal involvements are unusual in schistosomiasis, and adenopathy is absent. The laboratory findings when positive are diagnostic.

THERAPY

The therapy of this disease, as a result of the experience on Leyte and the follow-up studies in the United States, is in a state of flux. The treatment employed in the cases reported by me should not be considered ideal. Intramuscular injection of fuadin and intravenous injection of antimony and potassium tartrate were both used. Fuadin was given originally in a series of injections totaling 45 cc. of fuadin (0.36 Gm. of antimony) over a period of seventeen days. Reactions were negligible. Electrocardiographic changes were minimal in contrast with the changes induced by antimony and potassium tartrate. They appeared in less than 50 per cent of the cases after 35 cc. of the drug had been given. Later the dose was increased, because ova had been found to be present after the therapy. Antimony and potassium tartrate in a 1 per cent solution was employed in a series of fifteen intravenous injections over a period of twenty-nine days (0.73 Gm. of antimony). The solution was prepared daily and injected slowly without further dilution. Reactions consisting of severe cough, pain in the chest, vomiting and mild to moderate collapse were frequent and occasionally so severe as to induce a change to fuadin. Although symptomatically and in physical examination evidences of cardiac damages were not forthcoming, the electrocardiogram showed considerable change in nearly every case. Low voltage and inversion of T waves in several leads were prominent, but arrhythmias were not seen. The changes became manifest after 9 cc. of the solution (0.066 Gm. of antimony) had been given and frequently persisted for two and three months. It should be emphasized that in spite of these disturbing electrocardiographic changes subjective discomfort and evidences of cardiac involvement were not present clinically.

A review of the case reports indicates that the effects of both fuadin and antimony and potassium tartrate were beneficial. Improvement in the condition of all patients was noted at the conclusion of treatment. This short period of observation indicated that the amount of antimony given did not eradicate the parasite in all cases (case 3). One must conclude that prolonged observation is necessary for the determination of a cure and that an increase of the dose of the drug beyond that which was employed is indicated.

COMMENT

Residua involving the pyramidal and extrapyramidal tract and the cortex were present three months after the onset of disturbances of the

central nervous system. How long these defects will persist and how permanent they will be can be answered only by future study. Will scar formation and progressive fibrosis produce permanent secondary involvement?

There are two sources from which cases identical with those reported may arise in the United States: first, a group in which the disease may result from rapid air transportation from endemic areas and, second, a group in which the disease has been asymptomatic, undiagnosed or not entirely cured by treatment.

CONCLUSION

Schistosomiasis should be considered in obscure diagnostic problems, including neurologic disease suggesting encephalitis or multiple sclerosis, if the patient is a soldier who has returned to the United States from an area in which it is endemic.

Lieutenant Colonel M. G. Berry and Major A. S. Johnson supplied the data of case 1.

Colonel Henry M. Thomas Jr. helped in the preparation of this report.

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TESTS OF LIVER FUNCTION IN SCHISTOSOMIASIS JAPONICA

With Particular Reference to Antimony Treatment and With Report of Two Autopsies

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IT IS WELL known that repeated infection with schistosomiasis japonica may result in cirrhosis of the liver.[1] American soldiers who contracted this disease on the island of Leyte in the Philippines during the fall and winter of 1944 had but limited exposure to the cercariae of Schistosoma japonicum, so that their ultimate prognosis may be quite different.[2] During a serial study of tests of hepatic function in a group of 481 such patients, 2 died as a result of external violence about seven months after the onset of the disease, and their hepatic lesions were studied at autopsy, both grossly and microscopically. The observations on the hepatic lesions together with the results of tests of hepatic function done in relation to treatment in the whole group form the basis of this report.

REPORT OF CASES

CASE 1.—*Clinical.*—This 23 year old patient was exposed to the cercariae of Schistosoma japonicum in an endemic area sometime during a period of approximately ten weeks. He first had symptoms compatible with a clinical diagnosis of schistosomiasis at about the eighth week of this period, but ova of Schistosoma japonicum were not identified in his stools until ten weeks later. During the next three weeks he received 13.5 cc. of fuadin. Stools then became free of ova, but the exact time with reference to therapy is not known. Three weeks after completion of the course of fuadin the patient was seen in this hospital. The physical examination at that time showed no significant abnormality except for slight tenderness on deep palpation under the right costal margin. The patient com-

1. Strong, R. P.: Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases, ed. 6, Philadelphia, The Blakiston Company, 1942, p. 1429.

2. Mason, P. K.; Daniels, W. B.; Paddock, F. K., and Gordon, H. H.: The Latent Phase of Schistosomiasis Japonica, to be published.

plained of mild epigastric discomfort and slight generalized weakness. Eighteen per cent of the white blood cells were eosinophils. All tests of hepatic function were normal in result except one, which was repeated later and found to be normal. The tests and their values were: icterus index, 6; serum bilirubin, 0.3 mg. per hundred cubic centimeters; serum globulin, 2.9 Gm. per hundred cubic centimeters; cephalin flocculation, negative; bromsulfalein, 4 per cent, and the intravenous test for hippuric acid, 1.23 Gm. The value for the galactose tolerance test was 4.49 Gm., but when the test was repeated two months later the value was 2.49 Gm. A cutaneous test with Schistosoma mansoni antigen elicited a positive reaction. Five successive stool examinations beginning three weeks after completion of treatment with fuadin gave negative results, but six weeks later in a series of 6 more examinations of stools eggs of Schistosoma japonicum were identified. Treatment was begun with antimony and potassium tartrate, and at the time that the patient was accidentally killed by an automobile he had received eight doses or 152 cc. of a 0.5 per cent freshly prepared solution

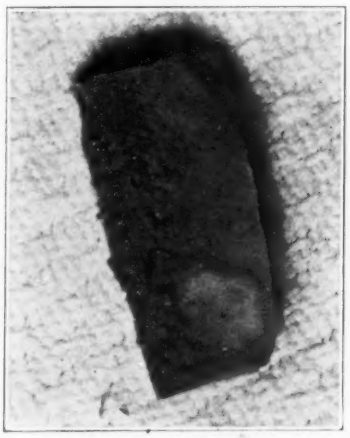

Fig. 1 (case 1).—Cut section of liver, showing largest nodule.

(antimony, 0.274 Gm.). Death occurred about seven months after the onset of the disease.

Autopsy.—A complete autopsy was performed. The cause of death was readily determined as being multiple fractures of the skull with laceration of the brain. Interest, however, centered in the lesions referable to schistosomiasis which were demonstrable in the jejunum, ileum, ascending, transverse and descending colon, and liver, all other viscera being normal. When the gastrointestinal tract was slit open numerous whitish yellow nodules of about pinhead size were found in the mucosa from the jejunum through the descending colon. In the ileum 35 and 40 cm. from the ileocecal valve there were two oval areas 3 by 1 cm. with depressed centers and rolled margins but with no frankly gross ulceration. The liver weighed 1,600 Gm. It was pale reddish brown and smooth except for a sprinkling of yellowish white nodules up to 0.3 cm. in diameter. On cut section similar nodules were found throughout. An example of the largest nodule is shown in figure 1.

Microscopic examination of the intestines and the liver showed two types of lesions: minute frank abscesses and pseudotubercle formations. Figure 2 shows a photomicrograph of a section through the transverse colon. The mucosa contains many leukocytes and lymphocytes but is not ulcerated. In the submucosa a typical abscess is seen. Centrally it is composed of degenerating leukocytes surrounding which there is a loosely woven fibroblastic network with heavy cellular deposition containing eosinophils, lymphocytes and plasma cells. Adjacent to the abscess is a pseudotubercle formation. It is of interest that within as small an area as one low power field the initial and presumably final

Fig. 2 (case 1).—Photomicrograph of a section through the transverse colon. × 400.

tissue response to an egg are seen. Figure 3 shows a photomicrograph of a submucosal pseudotubercle in which a distorted egg is clearly seen in the upper right portion. The hepatic lesions are similar to those described in the next case.

Case 2.—*Clinical.*—This 21 year old patient with schizophrenia committed suicide. He had been on Leyte where it was believed that he had contracted schistosomiasis japonica in December 1944. The diagnosis was established on a basis of clinical findings together with positive identification of Schistosoma japonicum eggs in the stool. Fuadin, 45 cc. (antimony, 0.392 Gm.), was given in a sixteen day period. Approximately six months later the patient was examined

in this hospital, at which time he did not have a palpable liver or spleen but did have tenderness along the right costal margin. There were no gastrointestinal complaints. A long blowing diastolic murmur was heard to the left of the sternum and systolic and diastolic murmurs over the apex (rheumatic endocarditis, old). The laboratory data showed that five successive stools were examined by direct smear, sedimentation, egg-hatching and zinc sulfate technics and were negative. A single specimen from sigmoidoscopy was also negative.

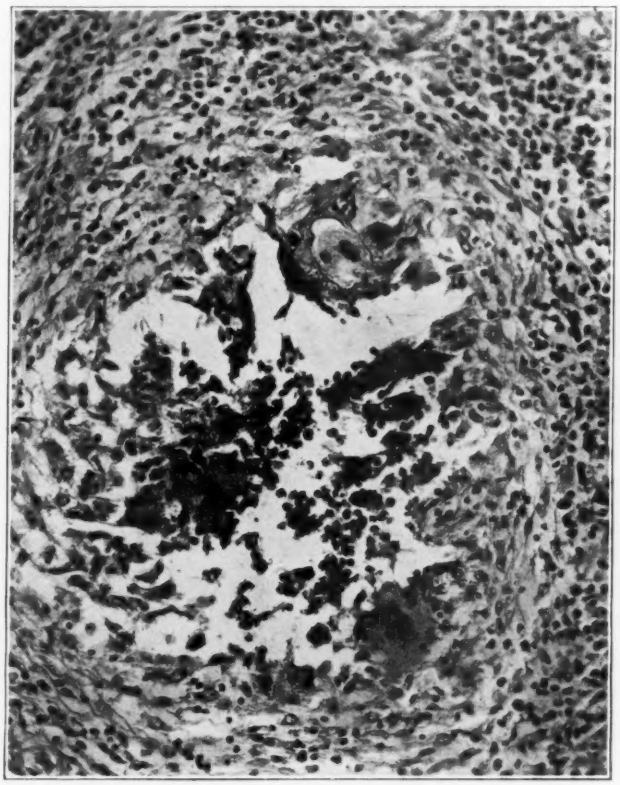

Fig. 3 (case 1).—Photomicrograph of submucosal pseudotubercles. × 400.

Twenty per cent of the white blood cells were eosinophilis, and the white cell count was 10,200. The nonprotein nitrogen was 32 mg. per hundred cubic centimeters, globulin 2.5 Gm. per hundred cubic centimeters, and the formaldehyde gel reaction negative. The icterus index was 4, serum bilirubin 0.1 mg. per cubic centimeter and the reading for the cephalin flocculation test with the Difco antigen was 2 plus. The bromsulfalein test showed 6 per cent retention of the dye stuff at forty-five minutes. From the combined clinical and laboratory data it appeared at the time of death that there were no symptoms or laboratory findings suggestive of active disease due to Schistosoma japonicum except

that there was still an eosinophilia and slight retention of bromsulfalein. Death occurred by strangulation about seven months after the onset of the disease.

Autopsy.—At autopsy it was obvious, as is seen in the photomicrographs (figs. 4 and 5), that there still was active hepatic disease. The liver weighed 1,674 Gm. and contained scattered small white nodules which were up to 3 mm. in diameter on the surface and up to 6 mm. in diameter in the liver substance. The surface of the liver was otherwise smooth. Similar nodules pre-

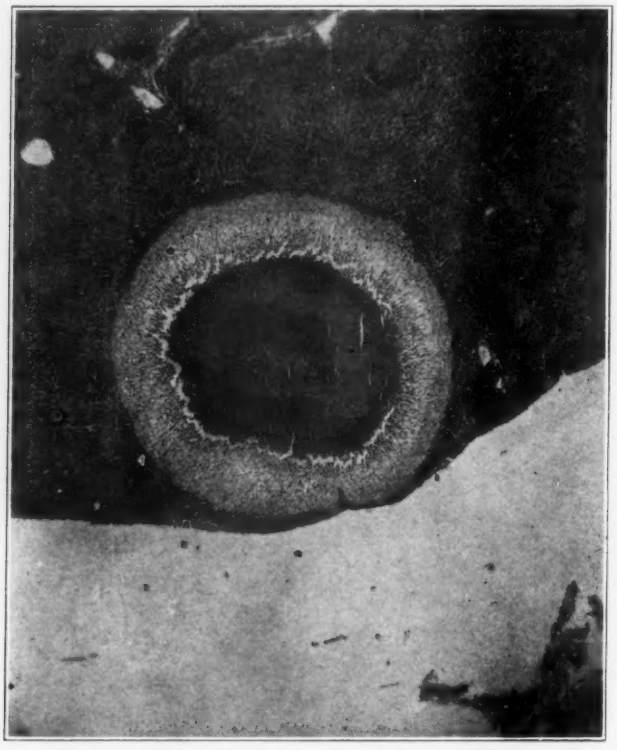

Fig. 4 (case 2).—Photomicrograph of liver showing circumscribed abscess. × 100.

sented themselves in the heart, in which there was gross evidence of mitral stenosis. The intestines apparently were normal, but no sections were taken by the prosector.

Microscopic examination of the liver showed that there were small circumscribed definite abscesses (fig. 4) with focal necrosis of parenchyma and also pseudotubercle formations (fig. 5) with partial fibrotic replacement characteristic of a healing phase. There was no fatty degeneration or evidence of a developing cirrhosis. Microscopic examination of nodules which grossly appeared like those in the liver was made from many areas of the myocardium. These

failed to disclose the presence of any abscess formation but there were focal areas with accumulations of large mononuclear cells, occasionally forming giant cells. No eggs were demonstrated in these collections. It was necessary to consider these formations as possible Aschoff bodies in view of the history of chorea and the mitral stenosis. Considering the length of time elapsed from the original episode, the cellular reaction was too extensive for Aschoff bodies.

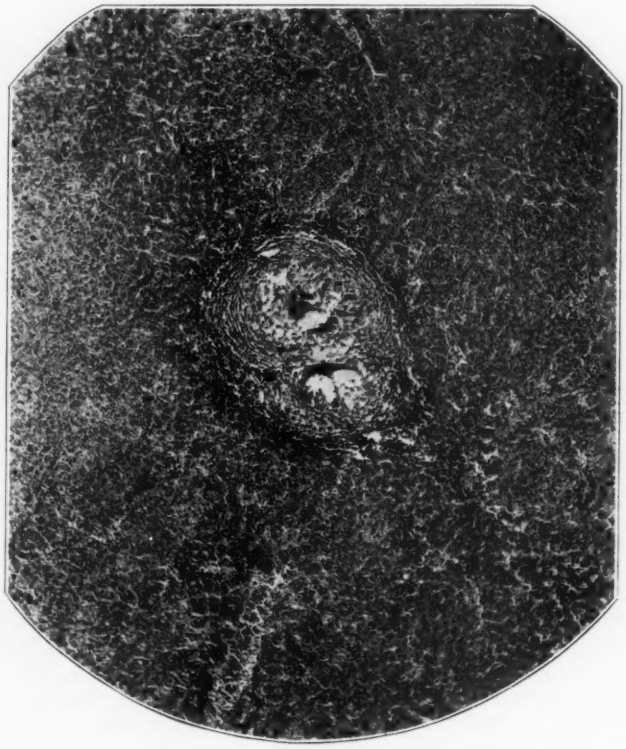

Fig. 5 (case 2).—Photomicrograph of liver showing pseudotubercle formations. × 50.

METHODS

Bromsulfalein.[3]—The amount of dye injected intravenously was 5 mg. per kilogram of body weight. The permanent standards used were supplied by Hynson, Westcott and Dunning. Since the standards were prepared for the 2 mg. test, the calculations were made by dividing the readings obtained by 2.5.

3. Todd, J. C., and Sanford, A. H.: Clinical Diagnosis by Laboratory Methods: Rosenthal's Bromsulfalein Method, ed. 10, Philadelphia, W. B. Saunders Company, 1943, p. 428.

Retention up to 4 per cent at forty-five minutes was considered normal.[4] However, in order to exclude all possible borderline values, in this study 8 per cent retention of the dye was considered to be the lowest abnormal value.

Galactose Tolerance Test.—Forty grams of galactose were given by mouth to fasting subjects. The amount of sugar excreted in the urine during the next five hours was determined by Benedict's quantitative method using a solution which had been standardized against galactose. The results were reported as galactose, and an excretion of over 3 Gm. in the five hour period was considered abnormal.

Intravenous Test for Hippuric Acid.[5]—Sodium benzoate (1.77 Gm.) was injected intravenously, and the urinary excretion of hippuric acid for a period of one hour was determined. Excretion of less than 0.80 Gm. was considered abnormal.[4] The hippuric acid was salted out of the acidified urine with ammonium sulfate (0.5 Gm. per cubic centimeter) at 20 C. for one hour. The precipitate was filtered with suction and was washed with three 5 cc. portions of ice cold water. In the calculation of the results, correction for the solubility of hippuric acid was made by adding 0.1 Gm. per hundred cubic centimeters of urine to the weight of precipitate obtained.

Icterus Index.—The color of the serum was compared with those of standard potassium dichromate solutions in 75 by 12 mm. test tubes. The serum was then diluted 1:2 and 1:3 with isotonic solution of sodium chloride, and the colors of these dilutions were matched with the standards as checks on the original value obtained. With an occasional serum, poor checks were obtained with the two dilutions, and in such a case the serum was diluted further until consistent values were obtained. A value of over 8 units was considered abnormal.[4]

Serum Bilirubin.[6]—The method used was the Thannhauser-Anderson modification of the van den Bergh test. The permanent cobalt sulfate standards of McNee and Keefer were used. A value of over 0.50 mg. per hundred cubic centimeters was considered to be abnormal[4]; however, in order to exclude all possible borderline values, in this study a value of 0.80 mg. per hundred cubic centimeters was considered to be the lowest abnormal value.

Urine Urobilinogen.[7]—A modification of the Wallace and Diamond serial dilution method was used on fresh morning specimens. Tests were routinely performed on a 1:5 dilution. Urine specimens yielding positive reactions in this dilution were diluted further and tested again. The highest dilution in which a positive reaction was obtained was recorded. A positive reaction in a dilution of more than 1:20 was considered abnormal.

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4. Lippincott, S. W.; Hesselbrock, W. B.; Ellerbrook, L. D.; Gordon, H. H., and Rhees, M. C.: Normal Values for Certain Tests of Liver Function in Healthy Soldiers, Am. J. Clin. Path., **16**:188, 1946.

5. Quick, A. J.: The Hemorrhagic Diseases and the Physiology of Hemostasis, ed. 1, Springfield, Ill., Charles C Thomas, Publisher, 1942, p. 325.

6. Thannhauser, S. J., and Anderson, E.: Methodik der quantitativen Bilirubin-Bestimmung in menschlichen Serum: Ueber die Ehrlich-Proschersche Reaction, Deutsches Arch. f. klin. Med. **137**:179, 1921. McNee, J. W., and Keefer, C. S.: The Clinical Value of the van den Bergh Reaction for Bilirubin in Blood, With Notes on Improvements in Its Technique, Brit. M. J. **2**:52, 1925.

7. Wallace, G. B., and Diamond, J. S.: The Significance of Urobilogen in the Urine as a Test for Liver Function, Arch. Int. Med. **35**:698 (June) 1925.

RESULTS OF TESTS OF HEPATIC FUNCTION

Initial Evaluation.—Results of tests of patients' hepatic function after arrival in this hospital are shown in table 1. All values for serum albumin were normal. The serum globulin values were elevated in 8 patients but only to a minimal extent and were considered inconsequential. As would be expected from this the formaldehyde gel test elicited a negative reaction in all but 1 case. At this time all but 4 per cent of the icterus index values and 6 per cent of the serum bilirubin values were normal. All tests for urobilinogen in the urine gave normal results. In the intravenous hippuric acid test, 5 per cent of the persons tested had a value below 0.80 Gm., but it has been shown [4] that even in normal persons occasional values below this level occur, usually because of incomplete emptying of the bladder. Four per cent of those given the galactose tolerance test gave abnormal reactions, but again the amount excreted above the normal was minimal.

TABLE 1.—*Results of Initial Tests of Liver Function on Return from Overseas*

Type of Test	Number of Men	Normal Tests		Abnormal Tests	
		Number	Per Cent	Number	Per Cent
Globulin	175	167	95	8	5
Formol gel	84	83	99	1	1
Icterus index	162	155	96	7	4
Serum bilirubin	246	231	94	15	6
Urobilinogen	85	85	100	0	0
IV hippuric	108	103	95	5	5
Galactose	189	182	96	7	4
Bromsulfalein	245	215	88	30	12

The most significant alteration of results in the hepatic function tests is seen in the bromsulfalein figures, in which 12 per cent of the patients had abnormal values. This test and that for serum bilirubin are discussed later in detail because of their relationship to treatment. In the 12 per cent of patients with initially abnormal bromsulfalein values and in the 6 per cent of patients with initially abnormal bilirubin levels, no correlation was found with jaundice, proved or suspected, during the acute phase of the illness overseas; with the presence of the eggs of Schistosoma japonicum in the stools examined at this hospital, or with symptoms on their arrival here. An elevated serum bilirubin during the initial evaluation, however, was associated three times as frequently with an abnormal bromsulfalein retention as was a normal serum bilirubin. Of 16 patients whose stools were repeatedly negative on examination in this hospital and who had varying degrees of abnormal bromsulfalein retention on initial evaluation, 10 on reexamination more than one month later gave normal reactions to the tests.

Bromsulfalein Test During Treatment.—The bromsulfalein test was performed on patients during and after treatment with two trivalent

antimony compounds (fuadin, and antimony and potassium tartrate), on patients whose stools were found to contain the eggs of Schistosoma japonicum (table 2, figure 6). The various courses of treatment lasted from twenty-five to forty-one days with injections of fuadin (intramuscularly) or of antimony and potassium tartrate (intravenously) being given every other day. The strength of the solutions used and

TABLE 2.—*Percent Incidence of Abnormal Reactions to Bromsulfalein Tests in Relation to Treatment at Harmon General Hospital*

		Number of Determinations					
					Days After End of Treatment		
	Result of Bromsulfalein Test	Before Treatment	During Treatment	End of Treatment	30-59	60-89	90 or More
Antimony and potassium tartrate 0.5% solution 320 cc.	0-4%	60 (90%)	56 (84%)	42 (65%)	31 (70%)	28 (67%)	9 (90%)
	6%	5 (7%)	5 (7%)	13 (20%)	5 (11%)	3 (8%)	0
	8% or more	2 (3%)	6 (9%)	10 (15%)	8 (19%)	11 (26%)	1 (10%)
	Number of patients	52	51	63	42	42	10
Antimony and potassium tartrate 0.5% solution 416 cc.	0-4%	22 (79%)	20 (66%)	10 (59%)	1 (33%)		
	6%	6 (21%)	4 (14%)	2 (12%)	2 (67%)		
	8% or more	0	6 (20%)	5 (29%)			
	Number of patients	24	20	13	3		
Fuadin 1st course 6.3% solution 65 cc.	0-4%	21 (64%)	14 (74%)	19 (44%)	13 (54%)	4 (40%)	1
	6%	6 (18%)	2 (10%)	9 (21%)	6 (25%)	2 (20%)	
	8% or more	6 (18%)	3 (16%)	15 (35%)	5 (21%)	4 (40%)	
	Number of patients	33	16	32	23	8	1
Fuadin 2d course 6.3% solution 65 cc.	0-4%	..	13 (62%)	7 (39%)	3 (37%)	5 (71%)	1
	6%	..	3 (14%)	5 (28%)	1 (13%)	2 (29%)	
	8% or more	..	5 (25%)	6 (33%)	4 (50%)		
	Number of patients	..	21	17	8	7	1
Fuadin 6.3% solution 105 cc.	0-4%	7 (47%)	8 (53%)	..	1		
	6%	5 (33%)	2 (13%)				
	8% or more	3 (20%)	5 (33%)				
	Number of patients	12	10	..	1		

the total amount given are recorded in the appropriate tables and figures. After the completion of a course of therapy, the patients were automatically released on a thirty day furlough, returning to the hospital for a follow-up period of two to three weeks followed by a second twenty day furlough before returning for their final evaluation. Tests of hepatic function were made at these times.

To patients whose stools were again found to contain the ova of Schistosoma japonicum during the follow-up period, treatment was

given a second time with the same course of therapy. Their bromsulfalein studies before the second course of treatment were among those in the follow-up period and were, therefore, on the whole higher than those before their initial treatment at this hospital. In figure 6 these are recorded in the appropriate follow-up period and are not included in the levels before treatment.

As can be seen in table 2 and figure 6, there was a distinct tendency for the incidence of abnormalities in the bromsulfalein test to increase significantly while treatment was being given, at the end of treatment and during the follow-up periods. The inclusion in the figures of borderline abnormalities added nothing to the general trend.

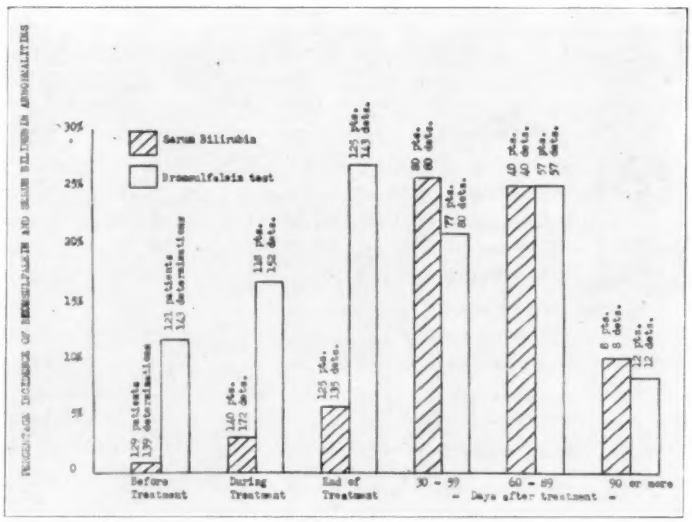

Fig. 6.—The relationship of the incidence of abnormalities in bromsulfalein tests and serum bilirubin concentrations to treatment at Harmon General Hospital. All types and courses of treatment.

In the few cases studied ninety or more days after the cessation of therapy, the incidence of bromsulfalein abnormalities had dropped to the level before treatment, but the number of cases is too small to justify any conclusions. In this regard, it is of interest that of 111 patients examined within three months after treatment overseas with fuadin, 10 (9 per cent) had abnormal reactions to bromsulfalein. Of 61 similarly examined more than three months after fuadin treatment overseas, 4 (7 per cent) had an abnormal reaction to bromsulfalein. All of 11 patients who had no treatment overseas gave initially normal reactions to bromsulfalein tests. The stools of 6 of these untreated patients were found to contain the ova of Schistosoma japonicum at this hospital.

In figures 7 and 8 are recorded individual cases followed through various courses of therapy. In each instance there were at least four determinations at different periods of study during the initial course. At each period only one determination per patient was recorded; if two had been done, the higher was recorded in each instance. In these individual cases repeatedly examined, the same general trend of the incidence of bromsulfalein abnormalities is noted as in the over-all picture, shown in figure 6. The same is true of the second course of the same therapy. The cases in which determinations were done during a third course of treatment at this hospital are too few to justify any conclusions.

TABLE 3.—*Percent Incidence of Abnormal Serum Bilirubin Concentrations in Relation to Treatment at Harmon General Hospital*

		Number of Determinations					
					Days After End of Treatment		
	Serum Bilirubin Results	Before Treatment	During Treatment	End of Treatment	30-59	60-89	90 or More
Antimony and potassium tartrate 0.5% solution 320 cc.	0-0.7 mg.%	66 (99%)	77 (96%)	64 (96%)	35 (74%)	18 (72%)	7
	0.8 mg.% or more	1	3 (4%)	3 (4%)	12 (26%)	7 (28%)	
	Number of patients	62	64	66	47	25	7
Antimony and potassium tartrate 0.5% solution 416 cc.	0-0.7 mg.%	28 (100%)	26 (81%)	14 (93%)	2		
	0.8 mg.% or more	0	6 (19%)	1 (7%)	1		
	Number of patients	24	22	14	3		
Fuadin 1st course 6.3% solution 65 cc.	0-0.7 mg.%	33 (100%)	27 (100%)	35 (97%)	15 (71%)	5 (63%)	
	0.8 mg.% or more	0	0	1 (3%)	6 (29%)	3 (37%)	
	Number of patients	32	26	29	21	8	
Fuadin 2d course 6.3% solution 65 cc.	0-0.7 mg.%	..	15 (83%)	14 (82%)	6 (75%)	7	1
	0.8 mg.% or more	..	3 (17%)	3 (18%)	2 (25%)		
	Number of patients	..	18	16	8	7	1
Fuadin 6.3% solution 105 cc.	0-0.7 mg.%	10 (99%)	12 (80%)	..	1 (100%)		
	0.8 mg.% or more	1 (1%)	3 (20%)				
	Number of patients	11	10	..	1		

It is clear from these studies that no obvious difference was demonstrated by the bromsulfalein test between the various types and courses of treatment.

Serum Billirubin During Treatment.—A quantitative serum bilirubin determination was made in almost every instance when the bromsulfalein test was done. The results of all such determinations are recorded in figure 6 and table 3 in the same manner as the results of the bromsulfalein tests.

Here again there was a distinct tendency for the incidence of abnormal serum bilirubin concentrations to rise in relation to treatment, but this

rise came later than that of the bromsulfalein, the major incidence occurring in the first follow-up period, on return from the thirty-day post-treatment furlough. Also again there is a tendency in the few cases followed for more than ninety days for the abnormalities to return to the level before treatment, with, however, too few cases to justify any conclusions. Determinations during the second course of treatment were recorded in the same way as for the bromsulfalein studies. The inclusion in the figures of borderline abnormalities added nothing to the general trend. It is interesting that, as compared with the pretreatment studies, no correlation was found to exist between the abnormal results of bromsulfalein tests and the abnormal serum bilirubin levels when contemporaneous determinations of these two were compared during treatment or during the follow-up period.

In figures 7 and 8 are also recorded individual cases followed through various courses of therapy with multiple determinations of the serum bilirubin concentration. The same method of recording these levels was used as in the results of the bromsulfalein test. It appears from these individual cases that the same general trend of the incidence of serum bilirubin abnormalities was present as in the over-all figure 6 with a definite trend for values of the serum bilirubin to increase with a passage of time in relation to therapy. Also it is apparent from these studies that no obvious difference was demonstrated by the serum bilirubin between the various types and courses of treatment. There was no indication that this was due to hemolysis because there was no apparent change in the erythrocyte count during or after treatment.

It is important to note in the studies of the results of the bromsulfalein and bilirubin tests that the degrees of abnormality were not great. Thus the majority of the bromsulfalein abnormalities were between 8 per cent and 12 per cent dye retention and the majority of the bilirubin abnormalities were between 0.8 and 1.2 mg. per hundred cubic centimeters. None was of the degree commonly associated with clinically severe hepatic disease.

COMMENT

In evaluating hepatic function in this group of persons it is important to consider the limited extent of the disease as shown by the findings in the 2 autopsies and the limited toxic effects associated with antimony treatment as noted in the results of the tests of hepatic function. The autopsy findings as illustrated in the photographs indicate clearly in our 2 cases of disease of seven months' duration, in which insufficient treatment [8] was given, that the hepatic lesions associated with seeding of eggs were circumscribed, tended to become fibrotic and left almost all of the liver intact. There was no indication of coalescence of lesions from

8. Schistosomiasis Japonica, United States War Department Technical Bulletin (TB Med 167), Washington, D. C., Government Printing Office, June 1945.

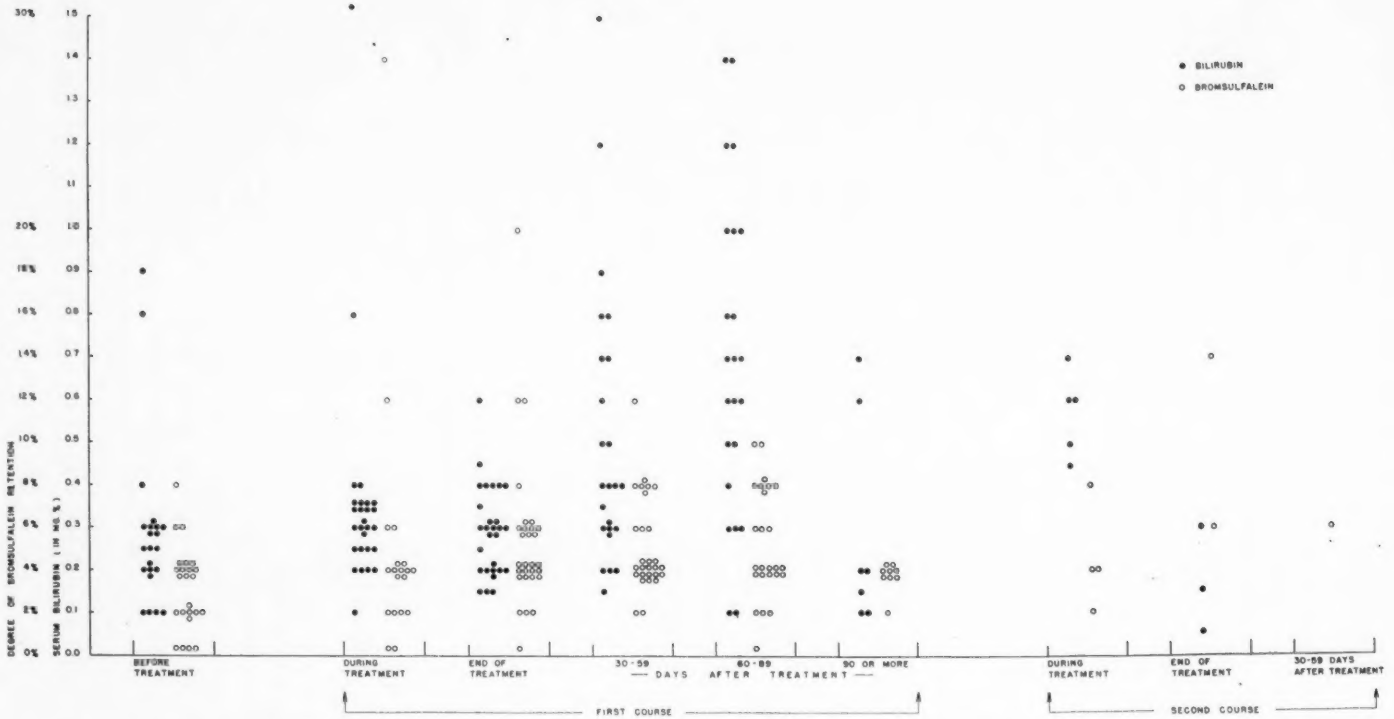

Fig. 7.—The relationship of bromsulfalein retention in 29 individual cases and of serum bilirubin concentration in 28 individual cases to treatment with antimony and potassium tartrate, 320 cc., at Harmon General Hospital.

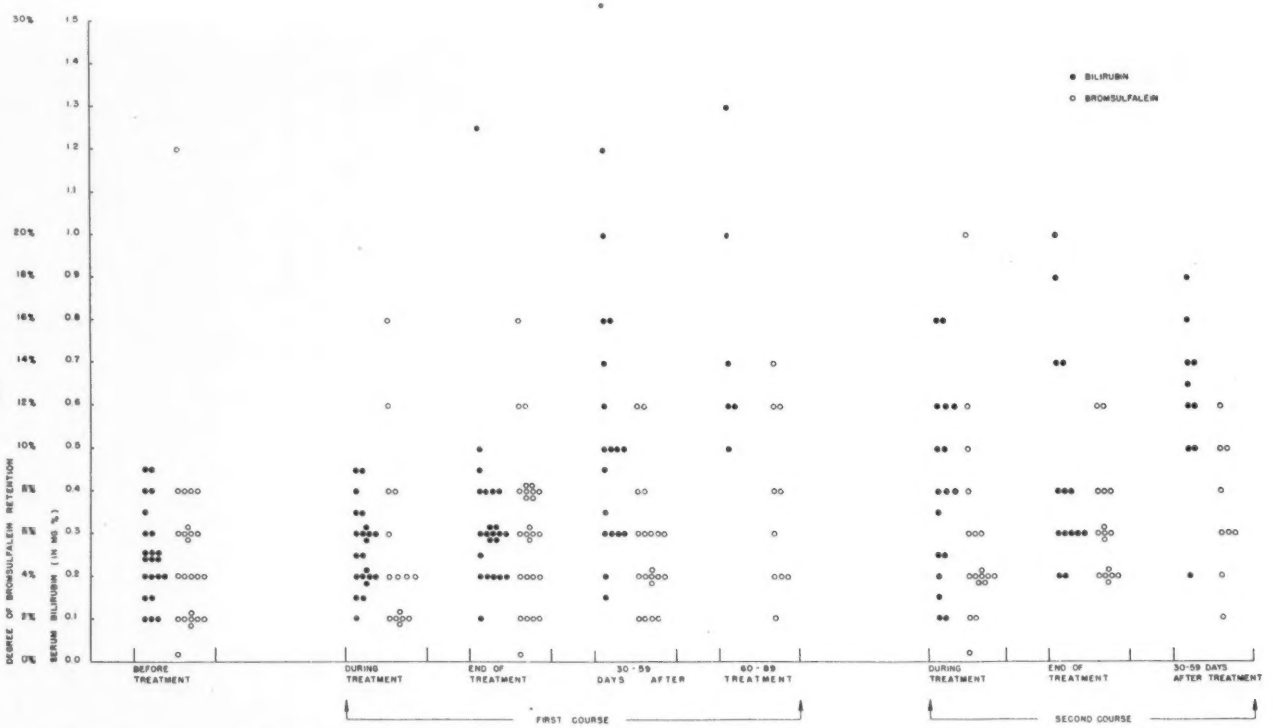

Fig. 8.—The relationship of bromsulfalein retention in 26 individual cases and of serum bilirubin concentration in 23 individual cases to treatment with fuadin, 65 cc., at Harmon General Hospital.

the portal spaces or extension of fibroblastic connective tissue to interrupt or isolate functioning lobules. In support of these pathologic findings are the initial studies of hepatic function which show a low incidence of dysfunction.

Whether the stated abnormalities in the results of the bromsulfalein tests and the serum bilirubin concentrations found in association with treatment are due to primary toxic effects of antimony[9] or are due to secondary effects is not known. It remains to be decided whether repeated courses of antimony can be given with impunity.

SUMMARY AND CONCLUSIONS

The pathologic lesions observed at autopsy in 2 patients in a group of 481 American soldiers with schistosomiasis japonica are presented together with the results of serial tests of hepatic function done before, during and after antimony treatment in a large number of these patients.

The lesions observed were in the large and the small intestine and the liver. They consisted of either minute frank abscesses or fibrotic nodules. One of the cases showed myocardial lesions possibly due to this disease. There was no indication morphologically in these 2 cases at this stage of the disease that damage to the liver sufficient to impair its function had occurred.

The initial studies of hepatic function in these patients on return to this country from overseas showed the following incidence of abnormal results: globulin, 5 per cent; formaldehyde gel 1 per cent; icterus index, 4 per cent; serum bilirubin, 6 per cent; urobilinogen, 0 per cent; intravenous test for hippuric acid, 5 per cent; galactose tolerance, 4 per cent, and bromsulfalein retention, 12 per cent.

Repeated bromsulfalein tests and serum bilirubin determinations showed a definitely increased incidence of mild abnormalities toward the end of and after treatment with trivalent antimony compounds. This increased incidence persisted for at least ninety days after the cessation of treatment. In a small group of cases followed beyond ninety days, the incidence was markedly decreased. The evidence suggests that antimony treatment has a minor direct or indirect effect on the liver.

9. Khalil, M.: The Specific Treatment of Human Schistosomiasis, Arch. f. Schiffs- u. Tropen-Hyg. **35**:1, 1931; cited by Schmidt, H., and Peters, F. M.: Advances in the Therapeutics of Antimony, Leipzig, Georg Thieme, 1938. Weese: Ueber experimentelle Nierenschaedigungen durch Fuadin und Brechweinstein, Abhandl. d. Med. u. Chem. **3**:412, 1936. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics, ed. 1, New York, The Macmillan Company, 1941, p. 748.

IMMERSION HYPOTHERMIA

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THE EFFECTS of freezing have been described in experimental hypothermia. The purpose of this article is to describe a clinical syndrome, herein to be called "immersion hypothermia," which is the result of immersion in the sea in latitudes where the temperature of the water is below approximately 65 F.

During the year 1944 approximately 150 men who had been immersed in the waters of the North Sea were seen by medical officers [1] at the United States Army Air Forces fighter station at Martlesham Heath, Suffolk County, England, all of whom contributed to the study of this problem. In all instances these patients were flying personnel of the United States Army Air Forces or Royal Air Force who had been on operational missions over enemy-occupied territory of the European continent. For a variety of reasons they were forced to abandon their aircraft by ditching [1a] or by bailing out into the North Sea. Most were picked up by rescue launches of the Royal Navy or the Royal Air Force and brought to the dock at Felixstowe, England, 8 miles (12.8 kilometers) distant from Martlesham, to which they were taken by ambulance. A few were rescued by Walrus amphibians of the Air-Sea Rescue Squadron of the Royal Air Force and flown directly to the airfield. Except for these few, most patients were not seen by a medical officer for several hours after the immersion.

The majority of the men showed no immediate effects other than temporary fatigue. In a statistical study to determine the factors involved in the survival of flying personnel whose aircraft became unserviceable over the English Channel and the North Sea, Mazer and Sheeley [2] collected the data on a large number of persons, including some of the data in the cases to be described here. Among 192 men picked up from

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1. These medical officers included Major Robert E. Nuernberger and Captains Walter Baumgarten, Roland Faulkner, Edward L. Higgins and Anthony Zachmyc as well as Squadron Leader Rouillard, of the Royal Air Force Station, Felixstowe, England.

1a. Ditching denotes the forced descent of an airplane on the water. The expression probably had origin in the reference to the North Sea as "The Big Ditch."

2. Mazer, M., and Sheeley, W. R.: Project no. 198, First Central Medical Establishment, U. S. Army Air Forces, Feb. 3, 1945.

various kinds of aircraft, 163 survived. Of the 29 who died, all but 3 were dead at the time of rescue.

The patients in the following reports of cases were all seen personally. Included are patients who demonstrated little pathologic change to contrast with those who showed a considerable amount despite a similar length and degree of exposure (table 1).

REPORT OF CASES

CASE 1.—The Liberator in which the patient, aged 20 years, was a crewman crashed into the North Sea, latitude 54° 04′ north and longitude 01°, 54′, 02″ east, at 12:53 p. m. on July 20, 1944. At 1:10 p. m. a launch reached the position. One other member of the crew (the patient in case 2 in this series) of the Liberator was rescued by this boat. Both men had been immersed in water with a temperature of 58 F. for approximately twenty minutes.

The patient was failing rapidly and swallowing a considerable amount of water when he was picked up. He was not unconscious but was extremely weak and was coughing. The pulse rate was reported as strong and regular. His memory was hazy for about six hours after the time of the crash. As soon as he was brought aboard he was placed in the prone position, then elevated by the hips to drain all the water which came from the mouth and then given artificial respiration (Schaefer method) for five minutes ("because of weakness and coughing"). His clothes were replaced by woollens, and he was covered by blankets. After a half-hour, during which he continued to moan and groan in apparent semiconsciousness, he quietly went to sleep. He woke four hours later, feeling much better. Before going to sleep he urinated and had a copious stool with passage of water (salt water?) from the bowel.

Six hours and twenty minutes after rescue he arrived at the Felixstowe pier and was taken immediately to Royal Air Force sick quarters. He was rational, well oriented, generally weak and somewhat pale and grayish. The skin felt normal. The oral temperature was 100.2 F. The pulse rate was obtained with difficulty, was slow and apparently regular and varied from 76 to 81. The arterial blood pressure ranged from 96 to 106 systolic and 54 diastolic. The heart rate was at first regular. The sounds were extremely faint. No murmur was heard. The systolic pressure came through the blood pressure cuff with irregular strength; for a time this irregularity was fairly constant as a failure of every fourth beat to manifest itself. Later the total arrhythmia became evident by cardiac auscultation. Over the medial portion of the lower lobe of the left lung there was hyperresonance and an absence of breath sounds. Lateral to this area was a region in which diminished vesicular breath sounds were heard. The diagnosis of auricular fibrillation and atelectasis of the lower lobe of the left lung was made clinically.

The patient was transferred by ambulance to the sick quarters at Martlesham Heath. At 8:40 p. m. (seven and a half hours after rescue) the temperature was 100 F., the pulse rate 76, the respiratory rate 24 and the systolic blood pressure 100. The diastolic pressure was unobtainable. One hour later the rate was around 100, and a loud diastolic murmur was heard over the precordium. After another half-hour (fifteen to twenty minutes after a cup of hot coffee was given) the pulse rate was strong and regular at 60 beats per minute. The heart sounds were strong, and the diastolic murmur was extremely soft and blowing in character. Because of the continually changing character of the cardiac observations and the continued irregularity with which sounds came through the sphygmomanometer cuff, it was thought that fibrillation might still be present.

TABLE 1.—*Summary of Important Clinical and Laboratory Data in Six Persons Rescued from Immersion in the North Sea*

Case	Name and Date of Immersion	Age, Yr.	Ball or Ditch	Time in Sea	Water Temperature, F.*	Time in Wet Clothes	Time After Rescue Before Observation, Hr.	Temperature on First Observation, F.	Pulse Rate	Blood Pressure	Psychic Changes	Blood Analysis	Electrocardiogram
1	S/Sgt. R. M. (July 20, 1944)	21	Ditch	20 min.	58	10 min.	8½	100.2 (rectally)	76 to 81	96 to 106/54	Semicoma	Normal	Auricular fibrillation and flutter
2	Sgt. C. A. (July 20, 1944)	23	Ditch	20 min.	58	10 min.	9	99.4 (rectally)	70	116/55	None	Normal	Not done
3	1/Lt. E. C. W. (Sept. 9, 1944)	23	Ball	40 min.	61	2 hr.	6	99 (orally)	84	130/34	Transient hysteria; semicoma, 1 hr.	Normal	Minimal prolongation of P-R interval
4	1/Lt. R. G. G. (Sept. 13, 1944)	25	Ball	60 min.	60	2 hr.	7	99 (orally)	60	96/56	None	Not done	Minimal prolongation of P-R interval
5	1/Lt. V. W. (Oct. 9, 1944)	22	Ball	40 min.	61	12 hr.	3	98.6 (orally)	82	128/88	None	Not done	Normal
6	1/Lt. H. H. L. (Dec. 29, 1944)	21	Ditch	35 min.	43	30 min.	½	93 (rectally)	68 to 102	95 to 120/ 70 to 85	Coma	Hemoconcentration; hypergiycemia	Auricular fibrillation and flutter

* Obtained from Meterological Branch, Royal Navy.

TABLE 2.—*Analysis of Blood Taken from Patients after Immersion in North Sea*

Case	Time After Rescue, Hr.	Hemoglobin Content, Gm./ 100 Cc.	Red Blood Cell Count	White Blood Cell Count	Differential Count			Specific Gravity (Whole Blood)	Specific Gravity (Plasma)	Plasma Proteins, Gm./ 100 Cc.	Hematocrit Reading, Vol./ 100 Cc.	Nonprotein Nitrogen (Whole Blood), Mg./ 100 Cc.	Creatinine (Whole Blood), Mg./ 100 Cc.	Sugar (Whole Blood), Mg./ 100 Cc.	Chlorides (Whole Blood), Mg./ 100 Cc.	Potassium (Whole Blood), Mg./ 100 Cc.	Phosphorus (Whole Blood), Mg./ 100 Cc.	Calcium (Serum), Mg./ 100 Cc.
					Neutrophils, %	Lymphocytes, %	Monocytes, %											
1	11	17.0	5,490,000	13,800	76	15	9	1.062	1.027	6.8*	50.0	28.8	1.5	100	476	..	4	11.1
2	11	15.5	.....	.....	..	..	..	1.059	1.027	6.8*	....	23.6	1.4	98	470	..	3.6	11
3	16	15.8	.....	.....	..	..	..	1.059	1.026	6.5	47.0	....	...	...	610			
6	½	16.4	5,060,000	15,900	25	75	0	1.063	1.031	8.2	48.5	40.0	...	308	482	26		
6	72	16.0	4,700,000	4,000	36	64	0	1.060	1.027	6.5	47.0	28.0	...	66	445	26.7		

* Protein partitions normal.

The chest was resonant and the breathing vesicular. His improved condition allowed for transfer to the Two Hundred and Thirty-First Station Hospital. On arrival there, twelve hours after rescue, he was calm, well oriented and without complaint. The heart rate was slow, 60 per minute, and there was slight irregularity. On the next morning, physical examination showed normality except for a few moist rales heard over both lungs posteriorly. The heart rate was regular at 70 beats per minute.

A roentgenogram of the chest made on July 21 showed small pneumonic areas in the lower lobes of both lungs. In the hospital the temperature never exceeded 99.5 F., and it was normal on the third day. The lungs cleared rapidly; a second roentgenogram of the chest, on July 25, showed clearance of the areas of pneumonitis noted on the patient's admission.

Although the surgeon at the hospital considered the heart normal, an electrocardiogram was taken twelve hours after rescue, because of the previous diagnosis of auricular fibrillation. It revealed auricular fibrillation alternating with impure flutter; the ventricular rate was 60 and almost regular in rhythm. A second electrocardiogram, twenty hours after rescue, showed normal sinus rhythm with a P-R interval of 0.20 seconds and normal QRS complex. A third electrocardiogram, six days later, was similar to the second one.

Blood drawn eleven hours after rescue was analyzed at the Sixty-Fifth General Hospital and yielded normal results (table 2). The urine showed no abnormalities.

The therapy was symptomatic, and recovery was uneventful. A month later the patient was reported by the surgeon of his squadron to be in good condition physically and mentally.

Summary.—The period of immersion was twenty minutes; the patient was failing rapidly and swallowing water when rescued. There were weakness and partial loss of consciousness during the first six hours. When first seen at the end of this time the patient showed clinical evidence of shock, auricular fibrillation and atelectasis of the lower lobe of the left lung. Auricular fibrillation and impure flutter were demonstrated by electrocardiogram twelve hours after his removal from the water. Normal sinus rhythm was present both twenty hours after and six days later. A roentgenogram showed small pneumonic areas in the lower lobe. Immediate therapy included artificial respiration, drying and application of warm coverings.

CASE 2.—The patient, aged 21 years (from the same aircraft as the patient in case 1), was immersed for the same length of time. He sustained several lacerations from the crash but was otherwise in good condition physically and mentally. He was cheerful, quiet and well oriented when first seen, six and a half hours after rescue. The heart was strong, loud and regular. No murmur was heard. The lungs were clear and resonant. The temperature was 99.4 F. by mouth, the pulse rate 70, the blood pressure 116 to 122 systolic and 50 to 30 diastolic. One hour later the temperature was 99 F., the pulse rate 100, the respiratory rate 20 and the blood pressure 116 systolic and 74 diastolic.

He was sent to the Sixty-Fifth General Hospital for admission. Blood taken for analysis approximately eleven hours after rescue yielded normal results (table 2).

A follow-up report from the surgeon of his squadron a month subsequent to immersion stated that the patient was in good physical and mental condition.

Summary.—The conditions of immersion were similar to those in case 1, except for addition of a wound sustained from the crash. No physiologic reaction was observed except for postimmersion elevation of temperature.

CASE 3.—The patient, aged 23 years, bailed out of his P-51 fighter plane at a height of 4,000 feet (1.2 kilometers) about 7 p. m. on Sept. 9, 1944. After being immersed in the North Sea for a few minutes, he got into his dinghy without difficulty. The Walrus aircraft reached him about 7 : 40 p. m. In trying to reach him the Walrus punctured the dinghy. He suffered a slight contusion of the scalp from striking the Walrus and was again immersed in the sea for a period of thirty minutes. The temperature of the water was approximately 58 F. He was reported to be hysterical and would not grasp a rope thrown to him. When finally pulled aboard he was shivering violently; the exposed parts of the body were cyanotic. Foam issued from the mouth during a short period of artificial respiration. He was wrapped in blankets and in a few minutes went to sleep (or lapsed into coma?). Thirty minutes later he woke, still complaining of the cold. The Walrus had been damaged and sank slowly, going under water just as the rescue motor launch hove to. The patient was unable to help himself. The master of the launch dove in and brought him to the boat. On board the launch he appeared to be in deep shock. He was pale and could not answer questions although he seemed to understand. He suffered from subjective cold sensations and shivering for an hour continuously and then for another several hours intermittently. He was dried, placed in warm clothing and given artificial respiration and 1 ounce (29.6 cc.) of brandy. He slept for several hours. When first seen by a medical officer, at 3 a. m. on September 10, his condition seemed good.

He was first under observation at station sick quarters on September 10, thirteen hours after rescue. His temperature was slightly elevated. The pulse rate, respiratory rate and arterial blood pressure were within normal limits. His mental status was normal except that he had no memory of events from the time of his being picked up by the Walrus to the later rescue by the launch. An electrocardiographic tracing taken over fifteen hours after he had been removed from the sea showed a P-R interval of 0.20 seconds as compared with a P-R interval of 0.18 seconds in a control tracing made two days later. Auscultation of the heart at the time of the first electrocardiogram revealed only somewhat distant sounds. Analysis of blood taken at the time the electrocardiogram was made gave essentially normal results.

Summary.—There was repeated immersion and rescue. Apparent severe shock, disorientation, amnesia and coma were evidenced. Fifteen hours later the patient had slight elevation of temperature, and possible prolongation of the P-R interval was seen in an electrocardiogram. Other findings were normal.

CASE 4.—The patient, aged 25 years, was first seen at 7 : 30 p. m. on Sept. 13, 1944, seven hours after being rescued by a Walrus aircraft. He had been sixty minutes in water, the temperature of which was 60 F. The airplane was unable to ascend from the surface of the sea, and subsequently the patient was transferred to a motor launch. The rescuing pilot noted that the patient's eyes were open but unseeing. The patient had loss of memory for a period lasting two hours. When the patient was seen, his temperature was 99.2 F. by mouth, his pulse rate 100, with regular rhythm and his blood pressure 108 systolic and 76 diastolic.

He was admitted to sick quarters a half hour later, in apparently good condition. He was somewhat excited and restless. No other psychic disturbance was observed. The temperature was 99 F. by mouth, the pulse rate 60 and the blood pressure 96 systolic and 56 diastolic. The first cardiac sound appeared muffled. The pulse was labile. At 9 p. m. the electrocardiographic tracing showed a rate of 94, regular sinus rhythm and a P-R interval of 0.22 seconds, with slurring of the QRS complex, which was, however, not prolonged. The

temperature level returned to normal next morning. A control electrocardiographic tracing made a month later showed a P-R interval of 0.20.

Summary.—Immersion was for sixty minutes. Neuropsychiatric signs were present during the first two hours after rescue, disappearing completely within a short time. There was slight transient prolongation of the P-R interval.

CASE 5.—The patient, aged 22 years, bailed out of his P-51 fighter aircraft shortly before dusk on Aug. 7, 1944 at longitude 51° 34′ 48″ north and latitude 02° 20′ 30″ east. He had to inflate his dinghy by hand and remained in the sea forty minutes (water temperature, 61 F.) before he was able to clamber into it. He floated in the dinghy for eighteen hours before rescue by a high speed launch of the Royal Air Force at 2:35 p. m. on August 8. After three hours on the launch he reached port and was seen by a medical officer. He had shivered throughout the night, but he felt better as soon as light dawned and he was able to dry his clothes and himself. On the launch he was given dry clothes, warm blankets and hot tea. When first seen, at 5:35 p. m. on August 8, he appeared in generally good mental and physical condition and had good color. The temperature was 98.6 F. orally, the pulse rate 82 and the arterial blood pressure 128 systolic and 88 diastolic. Auscultation of the heart revealed loud, distinct sounds and no murmurs. An electrocardiographic tracing at 8:20 p. m. was normal. No sequelae were observed.

Summary.—The patient spent forty minutes in the sea and eighteen hours in a dinghy during August. No ill effects were noted.

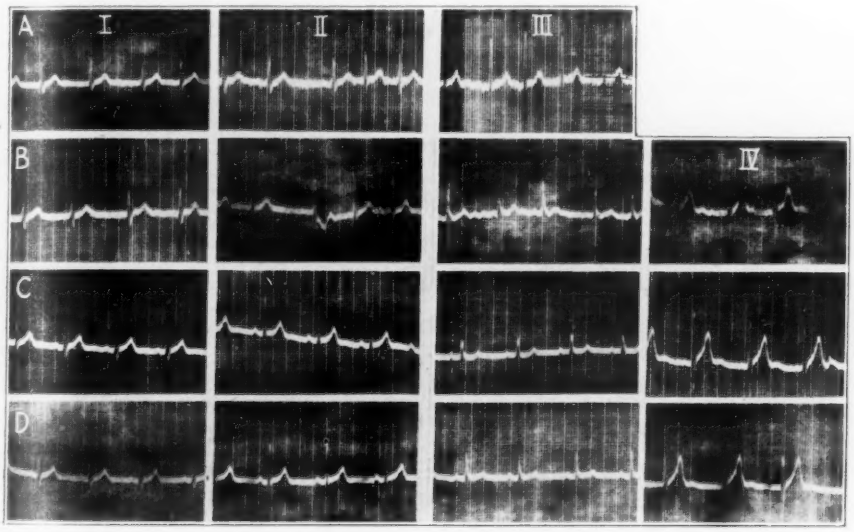
CASE 6.—The patient, aged 21 years, was returning from a combat mission when trouble developed in the cooling system of the P-51 fighter aircraft in which he was flying. He attempted to bail out but found that the airplane lost altitude steadily. At 12:45 p. m. he ditched the aircraft in the North Sea 4 miles (6.4 kilometers) due east of Orfordness, Suffolk County (52° 6′ north and 0° 40′ east). In the crash he struck the gun sight and sustained a laceration of the upper lip as well as a contusion of the parietal region of the scalp. He swam free of the airplane and remained in the water for over thirty minutes. His life vest functioned well, but he was unable to get into his dinghy. The water seemed extremely cold (43 F.). He grew weaker and felt that he could last only a few minutes longer. At 1:15 p. m. a Walrus aircraft reached him and after a few minutes pulled him aboard. His clothes were not removed, and he remained cold and wet.

The Walrus landed at Martlesham Heath airdrome at 1:45 p. m. The patient was taken immediately to sick quarters. His clothes were removed, and he was covered by warm blankets and given light massage. At this time he was unconscious. The fingers and toes were cyanotic. The skin was extremely cold and tightly drawn. There were intense shivering, rigidity and involuntary shaking movements, which intermittently attained the proportion of clonic contractions of the limbs. There was also extreme restlessness, which necessitated three to four attendants for restraint. The eyes stared blindly to the front. The pupils were widely dilated and did not react to light. The veins were partially collapsed. The rhythm of the heart was totally irregular, and the rate averaged 68. The sounds came through with varying intensity and in general were distant. The temperature, blood pressure and pulse rate could not be obtained at first. Auricular fibrillation was diagnosed clinically. The patient appeared moribund.

Treatment was begun at once. Warm blankets were placed around the patient and light massage given. Blood plasma was administered intravenously. A total of 4 units in 1,600 cc. of fluid was given from 2 to 3:30 p. m. Warming was

attempted by means of blankets, hot water bags and light massage. After about twenty minutes it appeared that these methods were not proving effective. A heat cradle was then placed over the patient to warm him more rapidly and the blankets removed. The patient became quiet enough for estimation of temperature at 2:30 p. m., seventy-five minutes after rescue from the sea, at which time it was 93 F. by rectum and axilla. An hour later it was 95 F. rectally. The temperature reached 100.8 F. by mouth in six hours and remained elevated until thirty hours after rescue.

The heart rate ranged initially from 68 to 102 and then remained between 60 and 75 for the first hour; the rhythm and intensity of contraction were totally irregular. The arterial blood pressure range was 95 to 120 systolic and 70 to 85 diastolic. During the next three to four hours the heart rate became more rapid, while the sound of the contractions gradually grew louder; a soft systolic murmur



Electrocardiograms of patient (case 6) taken at intervals after rescue from immersion in the North Sea. *A*, one hour after rescue. Auricular fibrillation is present. A short sequence of flutter waves is seen in lead III. *B*, five hours after rescue. Auricular fibrillation persists. In lead II there is a ventricular extrasystole. In lead III flutter is again evident. *C*, ten and one-half hours after rescue. Normal tracing with sinus rhythm. *D*, twenty-four hours after rescue. The electrocardiogram is normal.

was heard intermittently. Electrocardiograms (fig.) at one and five hours after rescue demonstrated auricular fibrillation with short periods of flutter, during which there was an auriculoventricular ratio varying from 3 to 5 to 1. The ventricular complexes remained normal in spite of the slow response of the ventricles to auricular stimulus. Ten and a half hours after rescue the electrocardiogram revealed sinus regularity with a rate of 80. The electrocardiographic picture remained normal during the following two days.

The patient recovered consciousness gradually between one and two hours after rescue. With the return of consciousness he became and remained rational.

Neurologic examination toward the end of this period revealed no localizing signs. There was no abnormal psychiatric behavior and no evidence of neurotic tendency during more than three days of observation. Blood was removed for analysis at the time of admission to sick quarters. The results are shown in table 1. The most extraordinary observation was the decided hyperglycemia, the blood sugar content being 308 mg. per hundred cubic centimeters. The leukocyte count was 15,900, with 25 per cent neutrophils, as compared with a control three days later of 4,000 with 36 per cent. The blood nonprotein nitrogen was 40 mg. per hundred cubic centimeters, compared with 28 mg. three days later. A specimen of urine taken two hours after rescue contained a small amount of albumin.

Summary.—The patient was in extremely cold water (43 F.) for over thirty minutes, followed by another thirty minutes chilled in wet clothes. Coma lasted two hours. Considerable shock, subnormal temperature, auricular fibrillation with failing heart rate, hemoconcentration, apparent inversion of neutrophil-lymphocyte ratio and tremendous elevation of the blood sugar content were noted. The temperature gradually rose to a hypernormal level, and it slowly returned to normal thirty hours later. The cardiac rhythm became normal between five and ten hours after treatment was begun. In addition to the generally accepted method of slow warming by means of warm blankets, hot water bags and massage, a heat cradle was used and 1,600 cc. of blood plasma was administered intravenously. Empirically, these two procedures seemed to be more effective than the others.

CLINICAL PICTURE

The pathologic changes encountered in the syndrome of immersion hypothermia are of a progressive type. Mild degrees occur in many patients who appear entirely well by the time they are seen by a physician, while patients with hypothermia of severe degree may die before they can be seen. It was fortuitous that the first patient described was observed at a time when changes were apparent. In slightly altered circumstances he would have been kept quiet overnight and sent to the hospital the following day. Here the diagnosis of atypical pneumonia would have been made (as it was), and the matter would have gone no further.

As it is, the laboratory investigations presented in this report were not made soon enough after rescue, except in case 6. From case 6 alone can one gain a consecutive idea of the pathologic physiologic changes present. However, personal observations on patients mildly affected by hypothermia and a study of the material gathered by the First Central Medical Establishment of the Eighth United States Army Air Force [2] fit well enough so that one may draw a general clinical pathologic picture. There are decided changes in the cardiovascular system. The heart rate is usually slow soon after rescue. The sounds are muffled, presumably as the result of a reduction of cardiac output. Arrhythmia of various kinds, including notably auricular fibrillation, as in cases 1

and 6, and prolongation of the P-R interval may be present. The arterial blood pressure is low; the radial pulse is difficult to feel. The diastolic pressure may be unobtainable when the systolic is extremely low. The pulse pressure is reduced. Because the ventricular rate is almost regular the rhythm may be considered as of sinus origin unless an electrocardiogram is taken. The auricular fibrillation seems to last for a number of hours, in 1 case between seven and ten and in another between thirteen and twenty hours.

In the 1 case in which blood was taken for analysis soon after immersion there was found tremendous hyperglycemia and mild hemoconcentration. Examination of blood drawn three days later yielded normal findings.

The temperature falls progressively during the immersion. It appears that a person who continues to wear wet clothing in a cold atmosphere is supercooled to almost the same extent as if he were still immersed in cold water. In case 6 the temperature was 93 F. by rectum one hour after rescue. Presumably it was lower at the time of rescue, but actual determination was prevented by the patient's violent hyperexcitability. In another hour the temperature had risen to 95 F. Within six hours it had reached 100.8 F. It then remained elevated until thirty hours after rescue.

Pyrexia following hypothermia of more than the mildest grade of severity seems to be a constant phenomenon, which persists for many hours. Since the external heat applied to most of the patients was only moderate in amount and was discontinued long before the body temperature returned to normal, it is thought that the fever may be a compensatory phenomenon, representing a specific reaction to hypothermia. The mechanism of this is unknown. It seems possible [3] that it originates in the central nervous system, perhaps in the temperature-regulating center.

The changes in the central nervous system include loss of consciousness, loss of memory and irrational behavior. These clear up as the acute condition subsides, although the period of amnesia may remain.

THERAPY

The treatment used followed the broad general principles applicable for shock. As far as possible, all patients were placed in a superheated room in bed. Wet clothes were removed immediately. The body was dried with warm towels. Warm blankets and hot water bags were

3. Grosse-Brockhoff, F., and Schoedel, W.: Das Bild der akuten Unterkühlung in Tierexperiment, Arch. f. exper. Path. u. Pharmakol. **201**:417-442 (June 12) 1943; abstracted, Bull. War Med. **4**:508 (May) 1944.

applied. Light massage of the arms and legs was employed, with doubtful results. In case 6 the utilization of a heat cradle over the nude body was thought to be a more effective method for the application of external heat than any of the aforementioned methods.

During the course of the six month period when observations were made on the patients in this series, the idea of the desirability of rapid reheating of the body, as contrasted with the generally accepted method of slow rewarming, evolved on an empiric basis. Rapid rewarming was long ago advocated by Lapchinski [4] and recently substantiated by Russian and German investigators.[5]

Conscious patients were given warm drinks such as tea and coffee in moderate amounts on an empiric basis and with the idea of providing local warmth in the region of the heart.[3] Whisky and rum were allowed, preferably well diluted with nonalcoholic drinks. Acute alcoholism was observed in 1 patient who was allowed 4 to 6 ounces (118 to 177 cc.) of rum by a well meaning sickberth attendant.

A total of 4 units of blood plasma (1,600 cc. of fluid) was given intravenously in the course of one and a half hours to the patient in case 6. He was the most seriously ill of all those encountered. When he was first seen he appeared moribund. At the end of one and a half hours of treatment, he had completely recovered consciousness and was feeling well. It is noteworthy that there was only a small output of urine despite the large intake of fluid. The experience in this case suggests that the use of blood plasma intravenously may be indicated in immersion hypothermia, as it is in shock. Theoretic considerations have been offered against administration of plasma in patients who have been cooled for several days (Talbott), but there are differences in the circulatory reactions of persons who are cooled rapidly and in those whose temperatures are kept at a low level.

The use of drugs was avoided in the treatment of these patients. Caffeine and nikethamide are probably not beneficial [6] as stimulants.

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4. Lapchinski, F. F.: Treatment of Frozen Limbs, Vrach., St. Petersb. **87**: 119, 1880; abstracted, Zentralbl. f. Chir. **15**:228, 1880.

5. (*a*) Scheiniss, B.: Death from Exposure to Cold, Moscow, 1943. (*b*) Weltz, G. A.; Wendt, H. J., and Ruppin, H.: Erwärmung nach Lebensdrohender Abkühlung, München. med. Wchnschr. **52**:1092, 1942. (*c*) Hozlohner, E.; Rascher, S., and Finke, E.: Bericht über Abkühlungsversuche am Menschen, secret report to H. Himmler, Oct. 16, 1942; translated, Alexander, L.: Treatment of Shock from Prolonged Exposure to Cold, Washington, D. C., Caducean Press, to be published.

6. Grosse-Brockhoff, F., and Schoedel, W.: Tierexperimentelle Untersuchungen zur Frage der Therapie bei Unterkühlung, Arch. f. exper. Path. u. Pharmakol. **201**:457-467 (June 12), 1943; abstracted, Bull. War Med. **4**:508 (May) 1944.

Atropine [7] reduces the vagal effect and elevates the arterial pressure. Intravenous use of dextrose [6] raises the blood pressure and supplies fluid. The use of epinephrine is definitely contraindicated. Grosse-Brockhoff and Schoedel [6] stated the belief that it reduces the arterial pressure in experimentally cooled animals. Rosenblum, Hahn and Levine [8] produced auricular fibrillation experimentally in hyperthyroid animals by amounts of epinephrine insufficient to alter cardiac rhythm ordinarily. Crismon [9] observed that small doses of epinephrine have an effect on cold animals far beyond that resulting in normal animals and that ventricular fibrillation may ensue. Kossman [10] stated that an "epinephrine effect" may occur spontaneously in experimental hypothermia in human beings, i. e., rise of the diastolic blood pressure with concomitant falling systolic pressure. It seems probable that the cooled heart responds abnormally to drugs. Among the reports of cases of immersion available for study [2] there occurred two deaths in which the data, although scanty, seem to confirm this. Each patient had had prolonged immersion during cold weather, 1 for forty-five minutes and 1 for one hundred minutes. Both died seven to nine hours after rescue. The treatment in each case included epinephrine given intravenously.

COMMENT

The clinical picture of immersion hypothermia is in general apparently similar to that of experimentally produced hypothermia. Under experimental conditions [11] the internal temperature of the body may be lowered to 75 F., with subsequent recovery. Changes occur early in the cardiovascular system. There is an initial rise of the pulse rate and arterial blood pressure, with a later fall in both, notable vasoconstriction, both arterial and venous, and increase in the viscosity of the blood. Later the pulse becomes imperceptible, the circulation time is prolonged to two or three times the normal and the blood volume is decreased. The auscultatory findings in the 2 patients with auricular fibrillation

7. Grosse-Brockhoff, F., and Schoedel, W.: Zur Wirkung der Analeptica auf unterkühlete Tiere, Arch. f. exper. Path. u. Pharmakol. **201**:443-453 (June 12) 1943; abstracted, Bull. War Med. **4**:508 (May) 1944; footnote 6.

8. Rosenblum, H.; Hahn, R. G., and Levine, S. A.: Epinephrine: Its Effect on the Cardiac Mechanism in Experimental Hyperthyroidism and Hypothyroidism, Arch. Int. Med. **51**:279-289 (Feb.) 1933.

9. Crismon, J. M.: Third Physical Fitness Conference, Sub-Committee on Clinical Investigation, Report no. 16, Washington, D. C., Oct. 5, 1943.

10. Kossman, C. E., and others: General Crymotherapy: Cardiovascular Aspects, Bull. New York Acad. Med. **16**:317-320 (May) 1940.

11. Talbot, J. H.: The Physiologic and Therapeutic Effects of Hypothermia, New England J. Med. **224**:281-288 (Feb. 13) 1941.

changed decidedly in rate, in rhythm and in type and intensity of the cardiac sounds while under observation. A transient diastolic murmur was heard in case 1. In case 6 a systolic murmur was heard intermittently. It is thought that these changes were caused by transient cardiac dilatation.

Auricular fibrillation and auricular flutter without other evidence of cardiac disease have been described clinically [12] and experimentally.[13] Such arrhythmias appear to be generally benign and are often transient. Cold has not been listed among the inciting factors of the clinical condition, although investigators of experimental hypothermia have encountered it fairly frequently.[14] According to Kossman abnormal rhythm is rare until the temperature drops below 85 F.

Friedlander and Levine [12b] considered benign auricular fibrillation without organic cause to be the result of a "trigger" phenomenon which may be of neurogenic origin. Hyperthyroidism has been cited as an illustrative condition, and epinephrine has been incriminated as the "trigger." Nahum and Hoff [13a] considered that fibrillation is produced by the interaction on the auricular myocardium of two factors: a predominant vagus activity and a specific exciting factor such as thyroxin. They were able to convert the normal cardiac rhythm of 4 hyperthyroid patients into auricular fibrillation by the administration of acetyl-beta-methylcholine. According to Bruenn [15] and Keith,[16] prolongation of the P-R interval in rheumatic heart disease is due to vagal activity. A high degree of correlation between the incidence of partial heart block and auricular fibrillation in various types of cardiac disease and in thyrotoxicosis was found by Altschule.[17] The two conditions occurred alternately in the

12. (*a*) Orgain, E. S.; Wolff, L., and White, P. D.: Uncomplicated Auricular Fibrillation and Auricular Flutter, Arch. Int. Med. **57**:493-513 (March) 1936. (*b*) Friedlander, R. D., and Levine, S. A.: Auricular Fibrillation and Flutter Without Evidence of Organic Heart Disease, New England J. Med. **211**:624-629 (Oct. 4) 1934. (*c*) Fowler, W. M., and Baldridge, C. W.: Auricular Fibrillation as the Only Manifestation of Heart Disease, Am. Heart J. **6**:183-191 (Dec.) 1930.

13. (*a*) Nahum, L. H., and Hoff, H. E.: Auricular Fibrillation in Hyperthyroid Patients Produced by Acetyl-B-Methyl-Choline Chloride, with Observations on Role of Vagus and Some Exciting Agents in Genesis of Auricular Fibrillation, J. A. M. A. **105**:254-257 (July 27) 1935. (*b*) Rosenblum, Hahn and Levine.[8]

14. Kossman and others.[10] Talbott.[11]

15. Bruenn, H. G.: Mechanism of Impaired Auriculoventricular Conduction in Acute Rheumatic Fever, Am. Heart J. **13**:413-425 (April) 1937.

16. Keith, J. D.: Overstimulation of Vagus Nerve in Rheumatic Fever, Quart. J. Med. **7**:29-41 (Jan.) 1938.

17. Altschule, M. D.: The Relation Between Vagal Activity and Auricular Fibrillation in Various Clinical Conditions, New England J. Med. **233**:265-266 (Aug. 30) 1945.

same patients, and both were thought to be the consequence of vagal activity. The afferent impulses producing vagal overaction on the heart in disease may arise from the root of the aorta, the great veins or the lungs.[17]

If one may assume that the cardiac arrhythmia of immersion hypothermia is the result of vagal overactivity, it is thought that it may be produced by the local effect of cold on the heart. There may be a specific sensitivity of some persons to cold, which predisposes to cardiac arrhythmia. The amount of sea water swallowed may be a factor. In both cases with auricular fibrillation (cases 1 and 6) there was evidence of a good deal of water being swallowed. That duration of immersion and temperature of the water are not the sole factors is evidenced by the difference between the patients in cases 1 and 2, both of whom were immersed at the same time for approximately the same length of time.

In experimentally induced hypothermia hemoconcentration may occur,[11] with a red blood cell count of 25 per cent above normal, a white blood cell count several times normal, an increase in polymorphonuclear neutrophils and a rise in reticulocytes. In case 6 of this series, comparison of blood removed at half an hour with that removed at seventy-two hours after rescue suggests confirmation of the elevation of the red and white blood cell counts. No explanation for the relative lymphocytosis is offered. Blood was drawn from the rest of the patients too late to be of significance.

The chemical constituents of the blood in experimental hypothermia are said to show little change.[18] The one chemical finding of importance in this series is the remarkably high blood sugar content found at first observation of the patient in case 6 (see previous remarks on the effect of epinephrine). The initial nonprotein nitrogen level in case 6 was moderately elevated.

In the causation of immersion hypothermia there are several emotional factors not found under the conditions of experimental hypothermia. The patients had been flying under constant strain for six to twelve hours, preparing for and engaging in combat and finding their way back to their bases under adverse conditions. In some there was a fear of flying over water. The realization of having to abandon the airplane and of being lost in the open sea, with the necessity of fighting against drowning, added to the emotional problem. The physiologic counterpart of this probably included the outpouring of increased amounts of certain physiologic secretions, including epinephrine.

Subsequent to the first draft of this paper there has been seen the summary of an extraordinary series of experiments, as yet unpublished,

18. Mazer and Sheeley.[2] Talbott.[11]

performed on human beings confined in German concentration camps.[4c] As the result of such experimentation on an allegedly large number of subjects, the German investigators concluded that the curve of rectal temperature of human beings chilled in water at 2 to 12 C. (35.6 to 53.6 F.) dropped slowly to 35 C. (95 F.) and thereafter more rapidly, with death at 27 to 26 C. (80.6 to 78.8 F.). Death was thought to result from cardiac failure, the damage being due to overloading of the heart caused by increase in viscosity of the blood and throttling of peripheral vascular districts. Auricular fibrillation occurred constantly when the rectal temperature dropped below 29 C. (84.2 F.). The prognosis was considered poor when the rate of fibrillation was slow and more favorable when the rate became faster. The blood sugar content rose in inverse proportion to the fall of the temperature. After removal of the patient from the water, the body temperature sank for fifteen minutes or longer. The most effective treatment was heat applied rapidly, best administered by means of immersion in a hot bath (temperature 40 to 50 C. [104 to 122 F.]). Heating by means of a cradle was considered decidedly inferior to immerson in a hot bath as a method of resuscitation but superior to all other methods. Drug therapy was not thought to be advisable. The administration of blood plasma was not discussed. The observations made in case 6, which is the only case in the present series in which the patient was seen immediately after immerson severe enough to produce unconsciousness, appear entirely compatible with the German data.

CONCLUSIONS

1. Immersion hypothermia is a progressive clinical syndrome which may follow immersion in cold water. It is related to experimental hypothermia and to clinical shock.

2. The clinical picture is the resultant of the coldness of the water, the length of the exposure, the emotional factors affecting the patient before and during exposure and the specific response of the person to cold.

3. The chief effects are those on (*a*) the cardiovascular system (among the transient conditions observed were auricular fibrillation and flutter, ventricular extrasystoles, slight prolongation on the P-R interval and falling arterial blood pressure, with narrowing of the pulse pressure), (*b*) the nervous system (partial to complete loss of consciousness and irrational behavior were observed) and (*c*) the blood (hemoconcentration and notable hyperglycemia were found in 1 case).

4. Treatment consists in rapid restoration of normal body temperature by external heat, minimal activity, administration of warm fluids by mouth and, in severe conditions, use of blood plasma. No drugs were used in this series. Use of epinephrine is contraindicated.

SUMMARY

1. Reports of cases are made of 6 patients who suffered from immersion in the North Sea on their return from long combat-flying missions.

2. Four of the patients had transient electrocardiographic abnormalities. One had abnormalities of blood chemistry.

3. The causation and therapy of immersion hypothermia are discussed, and the findings are compared with those in experimental hypothermia.

Progress in Internal Medicine

SYPHILIS

A Review of the Recent Literature

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(Concluded from Page 769)

STREPTOMYCIN IN SYPHILIS

Herrell and Nichols [196] have treated 4 patients with syphilis with 10,000,000 units of streptomycin given in divided doses over a period of ten days. In 3 cases of early syphilis results were negative at dark field examination after treatment, but in each case clinical relapse was observed. One patient with late gummatous syphilis had "temporary improvement."

Dunham and Rake [197] infected rabbits by the intracutaneous injection of T. pallidum and three days later gave to alternate animals intramuscular injections of streptomycin or crystalline penicillin G. The small amount of streptomycin that cured any of the rabbits when administered in divided doses over a four day period was 79,000 units per kilogram (375 mg. per kilogram) in one experiment and 187,000 units per kilogram (817 mg. per kilogram) in another. Since a comparable effect was obtained with 147 units per kilogram (0.088 mg. per kilogram) of crystalline penicillin G, it is concluded that streptomycin has spirocheticidal action but that penicillin G is more than three thousand times as effective.

FEVER THERAPY

Inoculation Malaria.

Historical.—Of interest to the historian is Bruetsch's [198] translation of Wagner-Jauregg's "The History of the Malaria Treatment of General Paresis." Priority for the use of malaria and relapsing fever in the treatment of dementia paralytica has been claimed [199] for Rosen-

196. Herrell, W. E., and Nichols, D. R.: The Clinical Use of Streptomycin: A Study of Forty-Five Cases, Proc. Staff Meet., Mayo Clin. **20**:449 (Nov. 28) 1945.

197. Dunham, W. B., and Rake, G.: The Activity of Streptomycin in Experimental Syphilis, Science **103**:365 (March 22) 1946.

198. Wagner-Jauregg, J.: The History of the Malaria Treatment of General Paralysis, Comment and Translation by W. L. Bruetsch, Am. J. Psychiat. **102**: 577 (March) 1946.

199. Priority in the Discovery of Fever Therapy in Psychoses, editorial, J. A. M. A. **124**:1061 (April 8) 1944.

blium. According to Wagner-Jauregg, however, "The facts, however, are that Rosenblium has never inoculated his patients with the idea of treating their mental illness. What he did was to make available his mental patients—among whom were no general paralytics—to the bacteriologist Motschutkoffsky, who in Odessa in the year of 1876 studied the transmissibility of recurrent fever to human beings. Subsequently, a few of these patients recovered from their psychoses and Rosenblium reported this later under an assumed name."[200]

Wagner-Jauregg, whose great contribution to syphilotherapy won him the Nobel Prize in 1927, acknowledges that the first suggestion to treat patients with mental disease with malaria was made in 1876 by Raggi,[201] who never put his idea into practice. Even earlier, indirect malaria therapy had been carried out by Galloni, director of an Italian institution for mental disease, who withheld quinine from psychotic patients who incidentally had contracted malaria, as he observed that such patients with mental disease frequently recovered from their psychoses.

The Clinical Aspects of Inoculation Malaria.—The clinical characteristics of the paroxysm from therapeutic infections with the McCoy strain of P. vivax are described by Kitchen and Putnam.[202] According to these investigators, the onset of therapeutic malaria may be characterized by a few days of continuous-remittent or quotidian or tertian intermittent fever, but, regardless of the type of onset, most therapeutic P. vivax attacks settle into quotidian periodicity. Among fifty-one attacks in this series, only one was tertian in character throughout. For some unexplained reason, the parasites are divided into two broods, whose maturation and sporulation times were separated by approximately twenty-four hours, thus creating quotidian activity. The behavior of the two cycles characterizing quotidian activity was similar with respect to all factors studied. The presence of rigor appeared to be an index of the severity of the paroxysms. The mean maximum temperature observed was 104.2 F. for six hundred and fifty-four paroxysms with rigor, while that for three hundred and forty-six rigorless paroxysms was 102.5 F. The maximum observed temperature being used as the marking point, two thirds of the paroxysms occurred between 3 and 8 p.m., thus disproving a common belief that malaria paroxysms occur chiefly during the morning. The authors state the belief that a change occurs in the host-parasite relationship at about the end of the first week of the attack.

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200. Oks, B.: Ueber die Wirkung fieberhafter Krankheiten auf Heilung von Psychosen, Arch. f. Psychiat. **10**:249, 1880.

201. Raggi, A.: Il processo febbrile nei pazzi, Riv.clin.di Bologna **6**:163, 1876.

202. Kitchen, S. F., and Putnam, P.: Observations on the Character of the Paroxysm in Vivax Malaria, J. Nat. Malaria Soc. **5**:57 (March) 1946.

Patients vary in their susceptibility to therapeutic malaria. These variations in susceptibility have been studied by Becker and his associates,[203] who have treated 300 patients in the United States Army for neurosyphilis, utilizing inoculation malaria. Their study corroborates the generally accepted opinion that Negroes and patients from the Mediterranean area are refractory to inoculation with P. vivax. It also was found that patients from endemic areas in Puerto Rico and the southeastern United States who have a history of malaria usually are less responsive to the tertian infection. Of the white patients, 208 were inoculated with P. vivax and 185 (90 per cent) had a satisfactory therapeutic course of ten or more paroxysms following primary inoculation. Some malaria therapeutists have been reluctant to inoculate natives of the southeastern United States with tertian malaria. Included in the present study were 43 white patients from this area, 80 per cent of whom proved to be susceptible. Of the 11 patients in whom the results were failures, all but 1 had had chills and fever at some time. Of those from the remainder of the United States, 93 per cent were satisfactorily treated with P. vivax.

Daily determination of the degree of parasitemia was found helpful in following the course of the infection as to its severity, degree of the patient's resistance and early forecasting of an immune response.

The problem of giving adequate malarial therapy to white patients with neurosyphilis who are partially immune to P. vivax infections is a provoking one. In order to complete a course of therapeutically effective malaria, reinoculations often are necessary. There are two objections to reinoculation with quartan malaria: (1) quartan reinoculation prolongs hospitalization because of the prolonged incubation period and the longer duration of the cycle, and (2) quartan infections not infrequently recur following antimalarial therapy. To study the problem, Kaplan, Read and Becker [204] made a cross inoculation study of malaria strain immunity with homologous and heterologous strains of P. vivax. Reinoculations with homologous strains produced minimal clinical activity. The duration of the homologous reinfection in this series of patients averaged 10.5 per cent of the duration of the original infection with the same strain. With heterologous strains of P. vivax (i. e., those differing in geographic origin from the original strain), reinoculation oftener produced therapeutically significant paroxysms. In the cross inoculation study, the duration of the heterologous reinfection averaged 74.3 per cent of the duration of the original infection. These authors

203. Becker, F. T.; Kaplan, L. I.; Read, H. S., and Boyd, M. F.: Variations in Susceptibility to Therapeutic Malaria, Am. J. M. Sc. **211**:680 (June) 1946.

204. Kaplan, L. I.; Read, H. S., and Becker, F. T.: Homologous and Heterologous Strains of Plasmodium Vivax: A Cross-Inoculation Study of Malaria Strain Immunity, J. Lab. & Clin. Med. **31**:400 (April) 1946.

state the belief that it is desirable to reinoculate with heterologous strains of P. vivax the white patients with neurosyphilis who prove to be partially immune to the originally inoculated strain. Completion of adequate courses of fever therapy without the use of quartan infections thus may be accomplished.

In most patients with active malarial infections there develop anemia and hypoproteinemia. Anemia usually is considered to be secondary to erythrocyte destruction, but no adequate explanation has been offered for hypoproteinemia. Feldman and Murphy [205] have studied the changes in blood volume associated with active untreated malaria to determine alterations in the total plasma protein contents and in the number of red blood cells. Simultaneous determinations of the plasma protein levels, plasma bilirubin level and erythrocyte concentrations were made so that the relative and total amounts might be calculated and compared. Blood plasma volume was found to be increased during the active phase of P. vivax and Plasmodium falciparum infections, reflecting the ability of the body to maintain a fairly constant blood volume in the presence of erythrocyte destruction. The increased plasma volume was disproportionately great after a paroxysm, thus exaggerating the degree of anemia. The calculated mass of circulating erythrocytes progressively decreased during P. vivax and P. falciparum infections and was in relation to an increase in plasma bilirubin levels.

Feldman and Murphy conclude that the normocytic anemia of clinically active malaria may be due to the two factors of erythrocyte destruction and hemodilution. The concentration of plasma proteins falls during the clinical phase of the disease, but the total amount of circulating plasma protein remains fairly constant.

Another explanation for at least part of the anemia and leukopenia so often observed in the course of therapeutic malaria is offered by Lanza.[206] In a study of the sternal marrow cellular components of 15 patients with acute malaria, this investigator found increases in the reticuloendothelial cells and in the plasma cells, regressive changes in the cells of the granulocytic series and an erythroblastic reaction proportional to the degree of anemia. These myelotoxic phenomena he believes are of significance in the genesis of malarial anemia and leukopenia.

Complications of Malarial Therapy.—The complications encountered in a series of 300 patients with neurosyphilis treated with therapeutic

205. Feldman, H. A., and Murphy, F. D.: The Effects of Alterations in Blood Volume on the Anemia and Hypoproteinemia of Human Malaria, J. Clin. Investigation **24**:780 (Nov.) 1945.

206. Lanza, G.: Citologia del midollo osseo nella malaria acuta, Pathologica **36**:31, 1944.

malaria are analyzed by Read and his co-workers,[207] who express the opinion that the more usual clinical features of malaria, i. e., anemia, lowered blood pressure, herpes simplex, gastrointestinal discomfort, muscular pain, cough and loss of weight should not be considered "complications."

Jaundice, edema, mild renal damage and peripheral neuropathy were encountered most frequently. Although these complications posed certain therapeutic problems, none was followed by permanent sequelae. Excessive red blood cell hemolysis in the absence of impaired hepatic function accounted for approximately 50 per cent of the cases of jaundice. Infectious hepatitis, serum jaundice and toxic hepatitis also were considered causes of this complication.

The precipitating cause of edema during active malaria oftenest was hypoalbuminemia, although 3 cases of unexplained edema were noted. Albuminuria and microscopic hematuria occurred frequently and were benign. Four cases of acute nephritis, supposedly due to the malaria parasite, were encountered. Three of the 4 patients received therapeutic quartan malaria, and the complication oftenest occurred prior to the fifth paroxysm. Two patients were classified as having diffuse glomerulonephritis, and 2 were considered to have focal embolic glomerulonephritis. The observed neuropsychiatric manifestations of P. vivax and Plasmodium malariae malaria were benign and readily amenable to antimalarial therapy. Two mental complications, one an agitated psychosis and the other an acute hallucinatory syndrome, may have been related to therapy with quinacrine hydrochloride (atabrine). In 13 patients there developed respiratory difficulty not due to pneumonitis. Severe and unexplained respiratory distress with cyanosis was observed in 2 cases. Bronchial asthma was decidedly aggravated during malarial paroxysms. Such unusual complications as perisplenitis, purpura, herpes zoster, urticaria, hyperlipemia, auricular fibrillation, spontaneous rupture of the spleen and hypocalcemic tetany are described briefly. In this series of 300 patients treated with benign tertian and quartan malaria there were two deaths, one due to rupture of the spleen and one to hypocalcemic tetany.

The medical literature contains many references to a variety of untoward effects of malaria on the cardiovascular system. Of the characteristics of malaria which might be expected to affect the heart are its chronic and recurrent nature, the systemic toxemia of the paroxysm, the anemia which is induced and occlusion of capillaries and arterioles in the coronary circulation.

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207. Read, H. S.; Kaplan, L. I.; Becker, F. T., and Boyd, M. F.: An Analysis of Complications Encountered During Therapeutic Malaria, Ann. Int. Med. **24**:444 (March) 1946.

Sprague's [208] experience during World War II indicates that malaria rarely causes cardiovascular damage. In none of several thousand cases of malaria did he observe any cardiac condition which could be specifically attributed to malaria. Any chronic disease, especially one resulting in anemia, may produce tachycardia, premature systoles or functional systolic murmurs, and malaria is no exception. A series of 50 cases of recurrent malaria, in all but 1 of which the condition was due to P. vivax, were studied electrocardiographically. Among the entire group there was no finding which could be considered outside the range of normal variation or of specific import. There were no deaths from acute cardiac disease or any proved chronic cardiac disease in this series. One would expect none, therefore, from therapy with inoculation malaria.

Grant [209] states the belief that malaria may incite several characteristic disturbances in various parts of the eye. The complications encountered, though mostly monocular, may be moderately incapacitating. The most frequent ocular condition encountered is herpetic keratitis, a nonspecific lesion. Lesions of the choroid, retina and optic nerve, which from histopathologic evidence appear to be due to emboli of parasitized red blood cells and which commonly are bilateral, appear to be the most serious of the complications from the standpoint of interference with vision. Results of treatment of these ocular disturbances with antimalarial drugs usually are successful, except in the case of herpetic keratitis, a virus disease for which specific chemotherapy is not available.

Bronstein and Reid [210] have been unable to confirm a previous report that all patients with malaria have abnormal hepatic function as measured by the cephalin-cholesterol flocculation test. They did find, however, indications of impaired hepatic function in approximately 75 per cent of the patients with malaria studied.

Cook and Hoffbauer,[211] who have studied hepatic function in 12 patients with therapeutic malaria before, during and after malaria therapy, also confirm the observation that there occurs transient but reasonably constant and readily detectable impairment of hepatic function. Four laboratory tests were used: the cephalin-cholesterol flocculation test, quantitative serum bilirubin test, quantitative Ehrlich reaction

208. Sprague, H. B.: The Effects of Malaria on the Heart, Am. Heart J. **31**:426 (April) 1946.

209. Grant, W. M.: Ocular Complications of Malaria, Arch. Ophth. **35**:48 (Jan.) 1946.

210. Bronstein, L. H., and Reid, R. D.: The Cephalin-Cholesterol Flocculation Test in Malaria, Proc. Soc. Exper. Biol. & Med. **31**:56 (Jan.) 1946.

211. Cook, C. D., and Hoffbauer, F. W.: Liver Functional Impairment in Therapeutic Malaria with Particular Reference to the Unsuccessful Use of Methionine as a Protective Agent, J. Lab. & Clin. Med. **31**:56 (Jan.) 1946.

and sulfobromophthalein test. Alternate patients, 6 of the 12, were given 8.1 Gm. of methionine orally per day in addition to a general diet. All 12 of the patients studied exhibited some evidence of disturbed hepatic function by one or more of the tests used. In 10 of the subjects, the abnormalities persisted from one to three days after the termination of the malaria. The addition of methionine to the diet failed to protect the liver.

Possibly the most spectacular major complication of malarial therapy, and certainly one of the most serious, is spontaneous rupture of the spleen. This accident, which, fortunately, is rare, has in the past invariably resulted in death. Moses,[212] however, has recorded a case in which early recognition of the condition and prompt surgical intervention resulted in recovery.

That acute psychoses of the paranoid type may follow therapeutic malaria is noted by Kaplan and his co-workers,[213] who have observed this complication of malarial therapy in a patient treated for apparently asymptomatic neurosyphilis. The problem of nonsyphilitic mental complications in patients with neurosyphilis is discussed, and it is indicated that considerable diagnostic confusion may arise when an attempt is made to differentiate syphilitic from nonsyphilitic psychoses in patients with positive cerebrospinal fluids, especially those treated with malaria.

Kitchen and Sadler [214] have reported that in a patient with dementia paralytica treated with inoculation malaria there developed an episode of blackwater fever. The attack lasted one week and was characterized by anemia, emesis, daily afternoon fever, hemoglobinemia, hemoglobinuria, proteinuria, bilirubinemia, icterus and near collapse. It is notable that this patient had been inoculated not only with P. vivax and P. malariae but, in an effort to obtain a satisfactory course of fever, with P. falciparum as well and that the parasites of malignant tertian malaria were known to have been present intermittently in the blood for a period of five months prior to the onset of hemoglobinuria. Had the original intention been to produce blackwater fever experimentally, it is doubtful whether a more satisfactory method could have been utilized.

Public Health Aspects of Inoculation Malaria.—From time to time there has been an uneasiness in public health circles that new foci for malaria epidemics may be created by the therapeutic inoculation of neurosyphilitic patients. However, after extensive study of the sub-

212. Moses, W. R.: Splenic Rupture in Therapeutic Malaria, South. M. J. **38**:745 (Nov.) 1945.

213. Kaplan, L. I.; Flicker, D. J.; Becker, F. T., and Read, H. S.: Acute Psychosis Following Therapeutic Malaria in a Case of Neurosyphilis, J. Nerv. & Ment. Dis. **102**:285 (Sept.) 1945.

214. Kitchen, S. F., and Sadler, G. G.: Report of an Attack of Blackwater Fever Subsequent to Induced Malaria, Am. J. Trop. Med. **25**:379 (Sept.) 1945.

ject, Bruetsch [215] concludes that, although there exists the theoretic possibility of accidental transmission of malaria from an artificially inoculated patient, malaria therapy, if properly managed, is not a practical menace to the public health. A critical review of the cases of malaria alleged to have originated from inoculation malaria indicates a lack of definite proof in almost all cases. The theory that the maintenance of malaria in the human host for prolonged periods by direct person to person inoculation leads to asexualization of the plasmodium is rejected in favor of the belief that unfavorable ecologic requirements adequately explain why accidental transmission practically never occurs.

Artificial Fever.

The Chicago Intensive Treatment Center group has further described the technic used by them for the administration of therapeutic fever by means of the hypertherm.

Craig, Buroker and Schwemlein [216] have discussed in detail the management of patients during the "induction period," stressing careful thermometry and the use of oxygen, fluids and sedation. During the induction period, the nurse-technician must be constantly alert for signs of cardiac or respiratory embarrassment and must keep close check on urinary function. The induction period ends when the rectal temperature reaches 105.8 F. if the desired temperature level is 106 F.

Describing the "maintenance" period of artificial fever therapy, Schwemlein, Buroker and Craig [217] note that the stabilization of the patient's temperature at the desired level is difficult, considerable experience being required to prevent "overshooting." In their experience, leveling of the patient's body temperature depends largely on the factors of skill of the nurse-technician, climatic conditions in the fever department, cabinet air temperature during the induction period, relative humidity of the cabinet air, induction period, weight of the patient, physiologic pattern (sic) and muscular activity of the patient.

Fever from Typhoid Pyrogens.

A purified pyrogenic antigen isolated from cultures of Eberthella typhosa has been found by Favorite and Morgan [218] to be a reliable

215. Bruetsch, W. L.: The Public Health Aspect of Malaria Therapy of Neurosyphilis, Am. J. Syph., Gonor. & Ven. Dis. **29**:494 (Sept.) 1945.

216. Craig, R. M.; Buroker, F. M., and Schwemlein, G. X.: Artificial Fever-Chemotherapy: V. Induction Period, Arch. Phys. Med. **26**:582 (Sept.) 1945.

217. Schwemlein, G. H.; Buroker, F. M., and Craig, R. M.: Artificial Fever-Chemotherapy: VI. Maintenance Period, Arch. Phys. Med. **26**:623 (Oct.) 1945.

218. Favorite, G. O., and Morgan, H. R.: Therapeutic Induction of Fever and Leucocytosis Using a Purified Typhoid Pyrogen, J. Lab. & Clin. Med. **31**:672 (June) 1946.

substance for the induction of therapeutic fever. These writers state the belief that the stability and uniformity of this pyrogen and its effectiveness in small single doses make it preferable to the whole typhoid-paratyphoid vaccine now commonly used. Temperature of from 103 to 105 F. followed the intravenous injection of from 0.001 to 0.002 mg. of this substance, but to obtain similar results with subsequent injections the amount of the pyrogen had to be increased threefold to fivefold.

Results of Fever Therapy.

From the careful histopathologic study of the visual pathways of 70 patients with all types of syphilis of the central nervous system, Bruetsch [219] deduces that the beneficial effects of malaria therapy in the control of syphilitic optic atrophy can best be explained on the basis that the degeneration of the optic nerves is due to a chronic inflammatory process which is arrested by malaria treatment. Despite clinical observation that primary optic atrophy is oftener observed in association with tabes dorsalis than with dementia paralytica, Bruetsch insists that the pathologic basis of the condition is more like that of paralysis (chronic inflammation) than that of tabes (degeneration). In his opinion, the reason that optic atrophy is not oftener observed in association with paralysis is that if untreated the latter is usually fatal before the ocular lesion has time to develop. Bruetsch finds malaria therapy more effective than mechanical hyperpyrexia in the treatment of optic atrophy, since he states the belief that he has found evidence that the "activation of the mesodermal tissue," which is produced by the malaria plasdomia and not by the elevated temperature, is responsible for the cessation of the inflammatory reaction. In view of the recent fad for surgical intervention to release adhesions resulting from optochiasmatic arachnoiditis, it is of note that this study indicates that in the majority of cases of syphilitic optic atrophy adhesive optochiasmatic arachnoiditis plays no part in the development or progress of the atrophy.

Lascara,[220] who has used both artificial fever and inoculation malaria in the treatment of neurosyphilis at the Central State Hospital, Petersburg, Va., favors artificial fever because, he states:

(a) The patients tolerate artificial fever therapy more readily; (b) patients can be treated on an ambulatory basis; (c) treatment complications are minimized; (d) the risks of inoculating an already ill patient with another infectious disease (malaria) are eliminated.

219. Bruetsch, W. L.: Malaria Therapy in Syphilitic Optic Atrophy, J. A. M. A. **130**:14 (Jan. 5) 1946.

220. Lascara, V. E.: Neurosyphilis with a Three Year Observation of the Comparative Therapeutic Effects of Inoculation Malaria and Artificial Fever Therapy, Virginia M. Monthly **73**:111 (March) 1946.

This author, whose findings are at variance with most previous reports, states that 84 per cent of the patients treated with artificial fever were improved, whereas only 48 per cent of the malaria-treated patients were benefited. In three months his mortality rate from artificial fever was 3 per cent and from inoculation malaria an amazingly high 22 per cent.

Knight and Schachat [221] summarize their experience with hyperthermia in the treatment of various syphilitic lesions of the eye. Fever therapy was supplemented with chemotherapy and the usual local ophthalmic therapeutic measures. Among 19 cases of primary optic atrophy, improvement was noted in 4 and clinical arrest of symptoms in 7. In the treatment of syphilitic choroiditis, the method was valuable, especially when the lesions were recent. Excellent results were obtained in 6 cases of acute iritis associated with secondary syphilis and in 4 cases of interstitial keratitis.

FEVER AS AN ADJUNCT TO PENICILLIN OR TO METAL CHEMOTHERAPY

In view of proposals to combine fever with metal chemotherapy or penicillin, a review by Fuhrman [222] on the effects of body temperature on drug action in general is timely. The effects of temperature on the action of drugs should be interpreted as to the rate, intensity and duration of action. The rate of action is determined by the time required for a drug to reach the site of action in sufficient concentration to produce its effect and by the time required for the interaction between the drug and (for example) a pathogenic organism. The time between administration and the appearance of effect is greatly influenced by the route of administration. Following intravenous administration, the effect of temperature is a result of the influence of fever on circulation time. Following subcutaneous or intramuscular injection, the rate of absorption is dependent on blood flow in the region of injection. The intensity of drug action largely depends on the concentration of the drug at its site of action, and this concentration in turn is the resultant of the processes of absorption, excretion and destruction within the body. All these processes may be influenced by changes in body temperature. Changes in toxicity (in terms of lethal dose) with changes in temperature may result from effects of fever on either the rate of absorption or the rate of elimination.

Oxophenarsine hydrochloride administered during fever is known to be more effective than is the same amount of the drug given in the

221. Knight, H. C., and Schachat, W. S.: Hyperpyrexia in Treatment of Ocular Conditions Due to Syphilis, Arch. Ophth. **35**:271 (March) 1946.

222. Fuhrman, F. A.: The Effect of Body Temperature on Drug Action, Physiol. Rev. **26**:247 (April) 1946.

absence of fever. One of the objections to combining fever therapy with this drug in the treatment of syphilis has been the lack of data as to how the toxicity of the arsenical is altered by fever. Boak, Dorn and Carpenter [223] have studied the effect of fever on the toxicity of oxophenarsine hydrochloride in rabbits. Their results, expressed in terms of maximal tolerated dose (MTD) and minimal lethal dose (MLD), indicate that the toxicity of the drug for rabbits is significantly increased by the combination. The maximum tolerated dose of oxophenarsine hydrochloride alone for rabbits, observed in this study to be 12 mg. per kilogram of body weight, approximates closely the mean of previous investigators. The reported figure for the minimal lethal dose (16 mg. per kilogram) is lower than the mean of previous studies. When oxophenarsine hydrochloride was injected either before or after physically induced fever, the maximal tolerated dose and the minimal lethal dose were lower than when the drug alone was administered. At the termination of the fever it was less toxic than when given immediately before fever. An increase in the length of the fever from three to five hours after the administration of the drug caused a further increase in toxicity. The weight and age of the animals appeared to influence the results, older and larger rabbits seeming more susceptible to the toxic actions of combined arsenofever therapy.

In 1944, Eagle and Musselman [224] showed that the spirocheticidal action of penicillin increases with the body temperature. Similar effects of hyperthermia on the bactericidal action of penicillin have more recently been reported by Hoyt, Pratt and Levine [225] and by Lee and Foley,[226] both of whom find the in vitro activity of pencillin against Staph. aureus to be enhanced at temperatures above 37 C.

Craig, Schwemlein and Kendell [227] report 20 cases of early syphilis treated with fever combined with penicillin. The amount of fever for each patient was three hours at 106 F., produced in an air-conditioned cabinet (hypertherm). The sodium salt of penicillin was administered prior to and during the course of the fever. Ten patients received

223. Boak, R. A.; Dorn, F. L., and Carpenter, C. M.: The Effect of Fever on the Toxicity of Mapharsen in Rabbits, Am. J. Syph., Gonor. & Ven. Dis. **29**:428 (July) 1945.

224. Eagle, H., and Musselman, A. D.: The Spirocheticidal Action of Penicillin in Vitro and Its Temperature Coefficient, J. Exper. Med. **80**:493 (Dec.) 1944.

225. Hoyt, R. E.; Pratt, O. B., and Levine, M. G.: The Activity of Penicillin at Temperatures Above 37 C., J. Lab. & Clin. Med. **30**:736 (Sept.) 1945.

226. Lee, S. W., and Foley, E. J.: Effect of Temperature on the Action of Penicillin in Vitro, Proc. Soc. Exper. Biol. & Med. **60**:133 (Oct.) 1945.

227. Craig, R. M.; Schwemlein, G. X., and Kendell, H. W.: Penicillin Combined with Fever Therapy: A Preliminary Report of Twenty Cases of Early Syphilis, J. Lab. & Clin. Med. **30**:1016 (Dec.) 1945.

300,000 units of penicillin in divided doses during the twenty-four hours of the prefever period and 300,000 units in divided doses during the fever, a total of 600,000 units. In 8 of these 10, results of treatment were failures (five clinical relapses, one clinical progression and two serologic relapses). Ten other patients received 600,000 units of penicillin before and 600,000 units during fever, a total of 1,200,000 units. Among these patients, the results of treatment in 2 were failures (both serologic relapses). The authors express the opinion that they have demonstrated that penicillin and physically induced fever may be safely combined in the treatment of early syphilis, that this form of therapy is less discomforting to the patients than arsenobismuth-fever therapy and that the results are "encouraging enough to warrant further study."

SYPHILIS IN THE POSTWAR WORLD

The available epidemiologic information indicates that the remarkable progress made in the control of syphilis in Europe during the interwar period has been wiped out completely since the beginning of World War II. It has been estimated [228] that syphilis in Europe increased tenfold during the war years. The only reliable indexes of the extent of the increase are those of the Scandinavian countries. In Norway, there appears to have been a sixfold increase in the incidence of syphilis since 1940, while in Denmark an eightfold increase is estimated. In such a predominately maritime nation as Norway, there are, as Guthe [229] notes, two important aspects of the problem: the problems of seamen exposed to the vicissitudes of a war-torn world and the complications engendered by German occupation. The incidence of syphilis in Sweden did not begin to rise until 1942, but since then the increase has ben accelerated.

In Germany, available data [230] suggest that the incidence of syphilis is nearly three times as high as that in Norway and Denmark. This is not surprising, since the licentiousness encouraged by Hitlerite Germany might well be expected to increase the incidence of venereal disease. Data from Switzerland [231] and from Greece [232] and unofficial reports

228. Rapid Increase of Syphilis in Europe, Epidemiol. Inform. Bull. **1**:403 (June 30) 1945.

229. Guthe, T.: Venereal Disease Control in Europe with Particular Reference to the Scandinavian Countries During World War II, Am. J. Syph., Gonor. & Ven. Dis. **29**:381 (July) 1945.

230. Venereal Disease in Occupied Germany, Epidemiol. Inform. Bull. **1**:801 (Nov. 15) 1945.

231. Pautrier, L. M., and Ullmo, A.: Récrudescence inquiétante de la syphilis dans le canton de Vaud et lacunes dans l'organisation de la lutte antivénérienne en Suisse, Dermatologica **92**:1, 1945.

232. Public Health in Greece During War and Occupation, Epidemiol. Inform. Bull. **1**:885 (Dec. 15) 1945.

from France, Belgium and Italy suggest that during the war years the incidence of syphilis increased significantly throughout the entire European continent.

Also to Soviet Russia,[233] where considerable success reportedly had resulted from a "planned" attack on venereal infections instituted by the Soviet regimen, hardships and mass migrations of war brought an increased incidence of venereal infection.

In the United States, trends toward an increased incidence of syphilis have been reasonably well held in check by intensified programs of civilian and military control. From an analysis of the results of blood tests taken during examination of men for the draft, Usilton [234] concludes that so far as the incidence of syphilis in the United States is reflected in the occurrence of positive serologic reactions among young men, in no section of the country was there any significant increase in the incidence of syphilis between January 1942 and July 1943, a period during which the war effort was expanding rapidly.

There has been an impression that during the recent years of war syphilitic infections among teen-age groups have constituted an increasing proportion of the problem of control of venereal disease. Seeking valid information on the point, Heller [235] has analyzed statistically data concerning patients admitted to public clinics for early syphilis from 1941 through 1944. The analysis was limited to women, since male admissions to clinics during this period were influenced by the war. The study indicates that a shift into the teen ages has not been nationwide, nor has it been constant from one year to another. Moreover, the areas affected were not the same for white persons and Negroes. Considering certain factors as possible causes for this disparity, the author found a tendency toward an earlier age of infection among white women in the presence of an increasing civilian population, particularly in areas of war-boom industrial concentrations. Increasing military populations seemed to have little or no tendency to be associated with an increased proportion of infections among teen-age white girls, presumably because of active control measures within the Armed Forces.

Postwar Syphilis Control.

The postwar problems of syphilis control in the United States have been carefully considered by the United States Public Health Service. The most immediate needs have been studied, and at a meeting of the state and territorial health officers the following recommenda-

233. Mashkilleison, L. M., and Rakhmanov, V. A.: Venereal Disease Control in the USSR, Am. Rev. Soviet Med. **3**:100 (Dec.) 1945.

234. Usilton, L. J.: Syphilis Among Civilians During World War II, January 1, 1942, Through June 30, 1943, J. Ven. Dis. Inform. **26**:263 (Dec.) 1945.

235. Heller, J. R., Jr.: Wartime Changes in the Age Distribution of Females Infected with Syphilis, Am. J. Pub. Health **36**:501 (May) 1946.

tions [236] were made: (1) that efforts be intensified to obtain increased cooperation of private physicians in control of venereal disease; (2) that new educational technics be devised and that a wider use of educational methods be made; (3) that the United States Public Health Service sponsor formal college training courses for investigators of venereal disease, to meet the serious lack of trained personnel; (4) that an evaluation of the present costs of performance of outpatient clinics be made, and (5) that the Rapid Treatment Center Program be made a permanent part of the general program and that inpatient care be extended to all syphilitic patients potentially responsive to intensive therapy, provided that this does not necessitate any curtailment of activity directed toward the control of infectious conditions.

The progress thus far made in implementing these recommendations is described by Heller.[237] Increased cooperation of private physicians has been sought by editorials in the *Journal of Venereal Disease Information* and by urging physicians to give increased attention to reporting cases and to accept the assistance of trained personnel from local health departments in obtaining and following up contact information.

Educational technics are being devised and extended chiefly through the work carried on at the Venereal Disease Educational Institute at Raleigh, N. C. The technics of mass education for intensive short time programs have been further developed. Plans are under way for three to nine month training courses for investigators of venereal disease. The development of inpatient rapid treatment centers lifted a good deal of the treatment burden from many outpatient clinics. An analysis of the costs and functions of clinics is in progress.

The Rapid Treatment Center Program, originally a temporary measure to prevent the spread of venereal disease among military personnel, has been continued. There now are over fifty centers operating throughout the country. In some instances in which it has been impracticable to build new centers, bed space in already existing hospital facilities has been rented.

The release from military service of millions of men might be expected to complicate the problems of civilian control of venereal disease. To minimize these complications, the Army [238] and Navy [239] have

236. Heller, J. R., Jr.: State and Territorial Health Officers Consider the Problem of Venereal Disease Control, J. Ven. Dis. Inform. **26**:168 (Aug.) 1945.

237. Heller, J. R., Jr.: The Postwar Syphilis Control Problem in the United States, J. Social Hyg. **31**:536 (Nov.) 1945.

238. Sternberg, T. H.: The Army Separation Process, J. Social Hyg. **31**:532 (Nov.) 1945.

239. Ferree, J. W., and Ennes, H.: The Venereal Disease Heritage of World War II: A Navy View of Demobilization and Postwar Venereal Disease and Social Hygiene Problems, J. Social Hyg. **31**:515 (Nov.) 1945.

instituted at their respective separation centers the following procedures: 1. All separatees are examined for evidence of venereal infection at the time of the final physical examination at separation. 2. Those with infectious or complicated venereal infections are retained in the service and treated until cured or noninfectious. 3. Serologic tests for syphilis are performed at the time of separation to detect cases of latent syphilis. The results of this test are reported to the United States Public Health Service, which via the state health departments notifies the veteran that further diagnostic studies should be carried out and, if necessary, antisyphilitic treatment instituted. Also, information concerning military and naval personnel who have been treated for syphilis while in service but who require further observation is furnished by the Army and Navy to the United States Public Health Service, which in turn forwards this information to the appropriate state health department.

VENEREAL DISEASE EDUCATION

In a report based on three years' study, a special advisory committee to the United States Public Health Service [240] outlines the general principles which should govern public education in control of venereal disease. Three of the committee's findings stand out: 1. Venereal disease education is a primary responsibility of official health agencies and should be conducted by them on an intensive but sustained basis. 2. Whenever possible, this education should be coordinated with other health education programs and so organized as to permit the active participation of interested groups and individuals within the community. 3. There should be a considerable expansion of facilities for training health department personnel who are to engage in venereal disease education, case finding and related activities.

Throughout World War II the Army had an unprecedented opportunity to study the results of the mass use of compulsory education in venereal disease. Larimore and Sternberg [241] describe the technics used and delineate their experiences and results. The aims of the Army's program were to impart technical knowledge about the venereal infections and to motivate the soldier to utilize this information at the time it is needed. Certain principles were found to be essential for the successful use of education as a part of the program for control of venereal

240. Report of U. S. Public Health Service Advisory Committee on Public Education for the Prevention of Venereal Diseases, J. Ven. Dis. Inform. **26**:256 (Dec.) 1945.

241. Larimore, G. W., and Sternberg, T. H.: Does Health Education Prevent Venereal Disease? The Army's Experience with 8,000,000 Men, Am. J. Pub. Health **35**:799 (Aug.) 1945.

disease: an integrated program; best possible quality and attractiveness of all educational materials; abandonment of the pedagogic concept of health education, with the substitution of an approach of "health advertising"; avoidance of overemphasis on sex, and technical accuracy of all educational materials. In motivation of a person to utilize the knowledge he has been given, fear, intelligence, pride and patriotism were found to be efficacious as appeals. Among the reasons for failure are listed the nature of the sex urge itself, sexy motion pictures, advertisements and illustrations, "war psychology," displacement of normal family and social relationships, newer methods of treatment, intemperate use of alcohol and low morale.

In measuring the results of the Army's educational program, the authors believe that the best single criterion is the extent to which prophylactic facilities are utilized. In November 1944, the Army required more than fifty million individual prophylactic items monthly. The utilization of this large number of prophylactics by an Army of eight million men is presumed to indicate favorable results from the educational program.

The results of an experiment in venereal disease education in Negro schools have been described by Carpenter and his fellow educators.[242] A preliminary survey of the knowledge on venereal disease possessed by students in seven Negro schools, comprising one thousand, one hundred and nineteen pupils ranging in age from 12 to 18 years, revealed an appalling lack of accurate information. Discussions with school instructors also revealed a lamentable paucity of factual information in the teacher group. As an informational device among Negro students, class discussion based on accurate information resulted in better learning than did the use of pamphlets and posters alone. All methods of approach used, however, resulted in a pronounced increase in the amount of information, although valid comparisons of the various teaching devices were not possible. It is of significance that there were no objections or criticisms encountered in this program to disseminate information on venereal disease to Negro students in junior and senior high schools.

Koch, Arnstein and Painter[243] discuss their experiences in industrial control of venereal disease in the San Francisco area.

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242. Carpenter, C. M.; Rahm, E.; Kirkendall, L. A., and Winchester, M. E.: An Experiment in Venereal Disease Education in Negro Schools, Am. J. Syph., Gonor. & Ven. Dis. **29**:392 (July) 1945.

243. Koch, R. A.; Arnstein, L., and Painter, A. C.: San Francisco Industrial Venereal Disease Educational and Case-Finding Program, J. Ven. Dis. Inform. **27**:9 (Jan.) 1946.

OTHER ASPECTS OF CONTROL OF SYPHILIS

A unique Alabama law requiring all persons between the ages of 14 and 50 to have serologic tests for syphilis has provided Denison and Smith [244] with the opportunity of observing the results of a short term, intensive campaign of case finding. After an extensive campaign of publicity and mass education and the establishment of suitable laboratory and treatment facilities, approximately 275,000 persons in Birmingham, Ala., were tested in a six week period. From among a population of 480,000, there were uncovered 569 patients with previously unknown early syphilis, 70 per cent of which was in women. The cost of each patient with syphilis found and treated was between $30 and $40. The authors state the belief that such short term case-finding campaigns are helpful in reducing the current mass of infectious venereal disease and that the procedure is practicable for the communities in which the rate of infection is high and in which adequate facilities for treatment and follow-up exist.

The usual contact interview has two objectives: (1) the general education of the patient regarding the disease, its prognosis, necessary treatment and the public health aspects and (2) following directly from the education regarding the public health aspects, the attempt to obtain identifying information about persons who may be infected through contact with the patient being interviewed. An attempt has been made by Hazlehurst, Stevick and Kahn [245] to go beyond these two objectives and, in addition to direct contacts, obtain from the patient the names of persons he or she may have reason to think may be infected for reasons other than direct contact with the patient. The fundamental defects inherent in this pernicious practice were promptly apparent, and, although fairly effective as a case-finding procedure, it was soon discontinued.

Prevalence of Syphilis.

The unique studies on syphilis in the Eastern Health District of Baltimore by Johns Hopkins University [246] have been further expanded

244. Denison, G. A., and Smith, W. H. Y.: Mass Venereal Disease Control in Urban Area, South. M. J. **39**:195 (March) 1946. Smith, W. H. Y., and Denison, G. A.: Blood Testing and Treatment Program in Jefferson County, Alabama, J. Ven. Dis. Inform. **27**:94 (April) 1946.

245. Hazlehurst, W. D.; Stevick, C. P., and Kahn, H. A.: Preliminary Report Evaluating the Worth of Obtaining Names of Suspected Contacts During a Regular Contact Interview, J. Ven. Dis. Inform. **27**:65 (March) 1946.

246. (*a*) Turner, T. B.: Studies on Syphilis in the Eastern Health District of Baltimore City: I. Principles Concerned in Measuring the Frequency of the Disease, Am. J. Hyg. **37**:259, 1943. (*b*) Turner, T. B.; Dyar, R.; Clark, E. G., and Birkhead, M. F.: Studies on Syphilis in the Eastern Health District of

by Clark,[247] who has determined the accumulated prevalence of syphilitic infection in this carefully enumerated population group, studying the influence of such factors as race, sex, age and socioeconomic status. These long range studies are based on two basic sources of data: records of population enumeration of residents of the Eastern Health District and records pertaining to the status of syphilis contained in an accumulative file on cases of syphilis and serologic status of patients. In general, the data make possible accurate quantitative determinations of the prevalence of syphilis in this locality, which eventually can be applied to accurate determinations of the trend of syphilis.

In the present article, the prevalence of known syphilis among white men was determined as 0.85 per cent and that of known syphilis plus history of treatment was 0.95 per cent of the population. Among white women, the prevalence of known syphilis was 0.70 per cent and that of known syphilis plus history of treatment 0.91 per cent. The highest rate among white men was in the 50 to 59 year age group and among white women in the 35 to 39 year group. Among Negro men the prevalence of known syphilis was 12.9 per cent; known syphilis plus history of treatment, 15.5 per cent, and estimated (on the basis of an additional and previously demonstrated to be pertinent factor), 19.5 per cent. Among Negro women, the prevalence of known syphilis, 16.2 per cent; known syphilis plus history of treatment, 19.3 per cent, and estimated, 21.0 per cent. In both Negro sexes, syphilis was most prevalent in the 35 to 39 year group.

Higher rates were found among divorced and separated persons than among those married or single. Figures for prevalence among persons classified according to the usual occupation of the head of the household showed little variation among white persons, although highest among the servant class. Among Negroes, on the other hand, the professional and proprietor class had a significantly lower rate than any of the other classes. This rate was 8.8 per cent, eight times higher than that of the

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Baltimore City: II. Discovery Rates as an Index of Trend, ibid. **37**:273, 1943. (*c*) Clark, E. G., and Turner, T. B.: Studies on Syphilis in the Eastern Health District of Baltimore City: III. Study of the Prevalence of Syphilis Based on Specific Age Groups of an Enumerated Population, Am. J. Pub. Health **32**:307, 1942. (*d*) Clark, E. G.; Turner, T. B.; Leiby, G. M., and Dyar, R.: Studies on Syphilis in the Eastern Health District of Baltimore City: IV. The Prevalence of Syphilis Among Parturient Women as an Index of the Trend of Syphilis in the Community, to be published. (*e*) Clark, E. G.; Cross, M. C., and Mason, J. S.: Studies on Syphilis in the Eastern Health District of Baltimore City: V. An Analysis of Serologic Tests Done from 1937-1939, to be published.

247. Clark, E. G.: Studies on Syphilis in the Eastern Health District of Baltimore City: VI. Prevalence in 1939, by Race, Sex, Age, and Socioeconomic Status, Am. J. Syph., Gonor. & Ven. Dis. **29**:455 (July) 1945.

white servant class. In general, the rates varied directly with educational attainment among both Negroes and white persons, the lowest rate being among persons with college education.

Economic Cost.

The suffering of the individual patient with dementia paralytica cannot be expressed in terms of dollars and cents, but the economic costs of this condition to the community can be approximated. According to Iskrant,[248] it costs the United States taxpayer at least $11,000,000 a year to maintain the paretic population of the nation. In addition, the annual loss of productive capacity (of paretic men only) approximates $112,000,000 a year. Further and incalculable expenses incurred by the community are the burden imposed on public and private charity for caring for paretic persons and their dependents, the cost of crimes committed by paretic persons and by the juvenile delinquency of their neglected children and financial losses caused by the wild speculation (sometimes with public funds) of some patients with early paralysis.

Historical Aspects of Syphilis.

At various times the destinies of mankind have been, as Podolsky [249] records, in the hands of rulers with syphilis of the central nervous system, and the disease significantly has altered the course of world history. This writer states the belief that the Tudors of England, Ivan the Terrible of Russia, Frederick the Great of Prussia, Louis IV of France and Mussolini, the Duce of Italy, all were conditioned in their actions by syphilitic involvement of the brain. How significantly these rulers influenced the expansion and national development or the political downfall of their respective countries is discussed.

Of the many theories of the origin of syphilis proposed by early observers, one of the most curious is to be found in the writings of an Englishman, George Sandys. The author, who was the seventh son of Edwin Sandys, Archbishop of York, was born in 1578. A great traveler, he visited many parts of Europe and the Near East and took part in the colonial development of Virginia. Although not a physician, he appears to have paid great attention to matters of medical interest encountered in his travels.

The following passage from Sandys' book, quoted by Riddell,[250] indicates the early belief that cannabalism was a factor in the early spread of syphilis throughout the Old World:

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248. Iskrant, A. P.: The Economic Cost of Paresis in the United States, J. Ven. Dis. Inform. **26**:175 (Aug.) 1945.

249. Podolsky, E.: The Syphilitic Brain and Human Destinies, M. Rec. **159**: 40 (Jan.) 1946.

250. Riddell, W. R.: An Old Theory of the Origin of Syphilis, Urol. & Cutan. Rev. **50**:144 (March) 1946.

I have read or heard how certaine merchants being bound to serve the *French* army at the siege of *Naples* with so many tun of Tunny, and not able to performe it; hearing of a late fought battell in *Barbarie*, repaired to the place, and supplied the quantitie of mans flesh drest in the same manner: which proued so over-high a feeding . . . that their bodies brake forth into lothsome vlcers; and from that infection the disease that taketh from them the name [Morbus Gallicus], not knowne before in our parts of the world, was introduced amongst us. And *Scaliger* . . . doth also affirme that it proceeded not originally from the impuritie of women, but from contaction; and that the *Spaniards* did first transport these rare wares from the *Indians*, as common amongst them as the measels amongst vs, and equally contagious. Which seemeth to confirme the former assertion, they hauing bene man-eaters for the most part.

SYPHILIS AND OTHER DISEASES

Yaws.—To what extent the immunity conferred by yaws protects against syphilis and vice versa is a question of considerable interest, which has not been fully elucidated by investigations with animals.

An experiment in which a patient with tertiary yaws (who received a total of 3.6 Gm. of neoarsphenamine but who remained seroresistant) was inoculated with T. pallidum from a patient with primary syphilis is reported by Findlay and Willcox.[251] After an incubation period of twenty-one days, a dark field positive chancre with a satellite bubo appeared. It thus would seem that this patient with persistent serologic evidence of yaws was capable of infection with the organism of syphilis.

A preliminary report on the penicillin treatment of 499 patients with primary and secondary yaws infections in Haiti has been made by Dwinelle and his Army associates.[252] Three schedules of therapy were used: Two hundred patients were hospitalized and given a total of 1,200,000 units of penicillin sodium over a period of four days. One hundred and fifty patients were treated on a two day ambulatory basis with penicillin calcium in beeswax and peanut oil. One hundred and forty-nine ambulatory patients received penicillin-beeswax-peanut oil in divided doses over a period of one day.

The clinical response was excellent. Primary and secondary lesions showed evidence of healing within twenty-four hours; pains in the joints disappeared in twenty-four to forty-eight hours, and plantar and palmar "crab" lesions became painless in forty-eight to seventy-two hours. The serologic response was less striking and somewhat less satisfactory than ordinarily occurs in penicillin-treated early syphilis. Whereas one would expect serologic reversal of 70 to 80 per cent of

251. Findlay, G. M., and Willcox, R. R.: A Human Experiment on the Relationship of Yaws and Syphilis, Brit. M. Bull. **3**:197, 1945.

252. Dwinelle, J. H.; Rein, C. R.; Sternberg, T. H., and Sheldon, A. J.: Preliminary Report on the Evaluation of Penicillin in the Treatment of Yaws, Am. J. Trop. Med. **26**:311 (May) 1946.

patients treated within six months in a group of patients with early syphilis who had received a similar amount of penicillin therapy, in only 10 per cent of these patients with early yaws was seronegativity attained.

The immediate clinical and serologic results obtained with penicillin-oil-beeswax appeared to be as good as those with the aqueous solutions. The authors point out that the development of a successful one day treatment schedule is of great practical value in countries such as Haiti, where large numbers of patients must be treated on an ambulatory basis in rural clinics.

Cancer of the Penis.—Because cancerous and precancerous lesions of the penis not infrequently enter into the differential diagnosis of syphilis, the review by Melicow and Gunem [253] is of interest. The prognosis of carcinoma of the penis is so poor and early diagnosis and radical operation so urgent that syphilotherapeutists would do well to follow these authors' advice to use caution in instituting antisyphilitic therapy in patients with atypical penile lesions. The delay incident to a therapeutic test may allow time for inoperable metastases. The differential diagnosis of carcinoma, leukoplakia, erythroplasia, Paget's disease and Bowen's disease is discussed.

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253. Melicow, M. M., and Gunem, E. J.: Cancerous and Precancerous Lesions of the Penis: A Clinical and Pathological Study Based on Twenty-Three Cases, J. Urol. **55**:486 (May) 1946.

REVIEW OF NEUROPSYCHIATRY FOR 1946

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IN RECENT years a great deal of work has been done on the psychologic aspects of mental disorder. The literature which has accumulated is enormous. Many writers have ignored the obvious fact that etiology is a complex question, that causes are multiple, and have said loosely that mental illness is psychologic or emotional in origin. A smaller, but persistent voice has also been raised, saying that much could be learned through biologic chemistry. Not much has been done about it but gradually good work in this field is accumulating. Folch [1] read a paper at the opening of a new research laboratory at the McLean Hospital in May 1946. He reviewed the contributions chemistry had made to psychiatry and outlined plans for the future. He explained that the brain has certain unique features: (1) lack of a lymphathic system, (2) abundant blood supply, with poor vasomotor control, (3) high consumption of oxygen, (4) specialized metabolism, (5) chemical composition different from other organs and (6) a mechanism separating the brain from the rest of the body, i. e., the blood-brain barrier. There is important recent work on several of these problems.

CEREBRAL BLOOD FLOW AND CONSUMPTION OF OXYGEN

The brain has a relatively great consumption of oxygen; in man it is second only to the thyroid in this respect. When the body is at rest the brain utilizes approximately one quarter of all oxygen consumed,[2] and about one fifth of the cardiac output goes to the brain. The arteriovenous difference in oxygen content is greater in the brain than in other organs. The brain not only can use oxygen at a high tension but it can extract oxygen from the blood when it is low in oxygen; for example, from venous blood. Under normal conditions the brain extracts about 40 per cent of the oxygen carried to it by the blood. When, therefore,

1. Folch, J.: Biochemical Problems Related to Psychiatry, in Psychiatric Research, Harvard University Monographs in Medicine and Public Health, no. 9, Cambridge, Mass., Harvard University Press, 1947.

2. Kety, S. S., and Schmidt, C. F.: Effects of Active and Passive Hyperventilation on Cerebral Blood Flow, Cerebral Oxygen Consumption, Cardiac Output and Blood Pressure of Normal Young Men, J. Clin. Investigation **25**:107, 1946.

the blood is low in oxygen, there is not enough for the brain, a state of affairs which rapidly results in impairment of cerebral function with such symptoms as syncope, stupor and convulsions. Further deprivation of oxygen causes irreversible lesions in the brain and eventually death.

Morrison [3] studied the brains of dogs and monkeys exposed to various degrees of anoxia. Not only was the effect of exposures to extreme degrees of anoxia studied, but the effect of repeated exposures to milder degrees of anoxia, not usually considered detrimental. For example, 1 dog was given thirty-three exposures of three hours each to atmospheres which caused the oxygen content of his blood to fall to 12 volumes per cent. He showed slight lesions in the gray matter. Another dog with 12 exposures at 9 volumes per cent showed pronounced lesions in both gray and white matter. With repeated exposures to mild hypoxia, it was observed that the first histologic changes occurred in the cell bodies of the cortical gray matter. This took place at a level of about 12 or 13 volumes per cent of oxygen in the blood if the exposures were long enough and were repeated often enough. When the percentage of oxygen was reduced still lower, to about 10 volumes per cent, and the number of exposures was increased, the white matter also became involved and presented a pattern of demyelination in the corpus callosum and in the white matter of the cerebral hemispheres. The lesions in their distribution and demyelination had a resemblance to those of Schilder's disease.

Nitrous oxide anesthesia is an alarming hazard at the present time, since want of oxygen is advocated deliberately to aid anesthesia. The available evidence indicates that nitrous oxide should never be administered with a concentration of oxygen below 20 per cent. The current use of anoxia as an adjunct to nitrous oxide–oxygen anesthesia has been the cause of death from asphyxia, psychoses from permanent damage of the brain, and defects of personality which may or may not be recognized.[4]

Schmidt [5] has shown that when the consumption of oxygen by the brain falls below half its normal amount, due to lack of oxygen supply through the blood, the lesions appear and are not reversible. This may occur in anoxia, shock or hemorrhage. In Schmidt's animals picrotoxin increased the consumption of oxygen by the brain to twice the normal amount if enough of the drug were used to cause convulsions. On the

3. Morrison, L. R.: Histopathologic Effect of Anoxia on the Central Nervous System, Arch. Neurol. & Psychiat. **55**:1 (Jan.) 1946.

4. Barach, A. L., and Rovenstine, E. A.: Hazard of Anoxia During Nitrous Oxide Anesthesia, Anesthesiology **6**:449, 1945.

5. Schmidt, C. F.; Kety, S. S., and Pennes, H. H.: Gaseous Metabolism of the Monkey Brain, Am. J. Physiol. **143**:33, 1945.

other hand, experimentally produced thyroid disturbances do not change the utilization of oxygen by the brain.[6]

Knowledge about the respiration of the central nervous system has been well reviewed by Quastel.[7] .He measured the metabolic rate of the brain by working on samples of excised tissue. Since then the metabolism of the brain has been estimated in vivo in laboratory animals and in man. Kety and Schmidt [8] recently developed a method of determining cerebral flow of blood in man. The subject inhaled a mixture of 15 per cent nitrous oxide, 21 per cent oxygen and 64 per cent nitrogen, with a mixture of calcium oxide and sodium hydroxide (soda lime) to remove the carbon dioxide from the closed system. Simultaneous samples of blood were drawn from an internal jugular vein and a femoral artery at approximately one, four, seven and ten minutes after the beginning of the inhalation of the gas. The samples of blood were analyzed for nitrous oxide, oxygen and carbon dioxide. From the values of nitrous oxide the cerebral blood flow can be calculated, and from the other values the difference in the oxygen content of the cerebral arteries and the cerebral veins can be determined. With these data in hand the metabolic rate can be figured in terms of consumption of oxygen per hundred grams of cerebral tissue per minute. The metabolic rate is found to be about 3.7.

Gibbs, Maxwell and Gibbs [9] have measured cerebral blood flow by injecting a dye into an artery supplying the brain and determining its concentration in the returning venous stream. They did this in several human cases and checked it against a direct volumetric measurement of blood flow in 1 case. They found that the average flow is 617 millimeters per minute and computed the average consumption of oxygen as 39.2 millimeters per minute. Figured as cubic centimeters per hundred grams of brain tissue per minute, this gives a result of about 3 for a metabolic rate. This is considerably lower than the figure of Kety and Schmidt, but at least it is within the same range, and the differences will have to be explained when the technics have been used on larger numbers of subjects. At least there are now available an approximation of what the human cerebral blood flow is and a fairly accurate determination of cerebral metabolism. Gibbs found that hyper-

6. Fazekas, J. F.: Cerebral Metabolism of Hyperthyroid, Thyroid Deficit and Cretinous Rats, Federation Proc. **5**:26, 1946.

7. Quastel, J. H.: Respiration in Central Nervous System, Physiol. Rev. **19**:135, 1939.

8. Kety, S. S., and Schmidt, C. F.: Determination of Cerebral Blood Flow in Man by the Use of Nitrous Oxide in Low Concentration, Am. J. Physiol. **143**:53, 1945; footnote 2.

9. Gibbs, F. A.; Maxwell, H. P., and Gibbs, E. L.: Volume Flow of Blood Through the Brain of Man at Rest, During Hyperventilation and While Breathing High CO_2, Federation Proc. **5**:33, 1946.

ventilation greatly reduced blood flow and that inhalation of carbon dioxide increased it.

Himwich and his colleagues [10] used the methods of Kety and Schmidt to study the metabolism of the brain during pentothal anesthesia. In normal controls Himwich found the metabolic rate to be about 3.3 cc. of oxygen per hundred grams per minute. This is about halfway between Gibbs's figures and those of Kety and Schmidt. With the subject under pentothal anesthesia the values fell to 2.1 cc. during the third stage of anesthesia. Obviously cortical excitation is depressed, and this is probably the main cause of narcosis, but comparison with patients suffering from metabolic depression in hypoglycemia coma [11] suggests that pentothal also directly depresses nerve function.

All of these observations both on animals and man deal with the oxygen consumption of the brain, considered as a single organ. They do not take into account the fact that the vascular structure of any given region of the brain is in proportion to its metabolic demands. Evidence for this is put forward by York, Homburger and Himwich [12] from the physiologic side. It has long been known that gray matter and certain nuclei in the brain had a much richer capillary network than white matter.[13] The idea that the observed quantitative differences in the capillary bed are related to metabolic activity is based on good evidence. In some areas in which nerve cells were not abundant but capillaries were, the discrepancy has been explained by the great number of synaptic structures in these areas even though nerve cells were present in only moderate numbers.

Mitochondria are found to be abundant where the nerve cells and their dendrites (neuropil) are highly vascular. Scharrer [14] has studied this by combining injection of the capillaries with especial stains for mitochondria. The correlation between density of capillaries and abundance of mitochondria appears to be the expression of a functional relationship. This fits in with Campbell's [15] observation that oxidase

10. Himwich, H. E.; Homburger, E.; Maresca, R., and Himwich, W. A.: Brain Metabolism in Man: Unanesthetized and in Pentothal Narcosis, Am. J. Psychiat., to be published.

11. Himwich, H. E., and others: Cerebral Blood Flow and Brain Metabolism During Insulin Hypoglycemia, Am. J. Physiol. **132**:640, 1941.

12. York, G. E.; Homburger, E., and Himwich, H. E.: Similarity of Cerebral Arteriovenous Oxygen Differences on Right and Left Sides in Resting Man, Arch. Neurol. & Psychiat. **55**:578 (June) 1946.

13. Craigie, E. H.: Architecture of the Cerebral Capillary Bed, Biol. Rev., London **20**:133, 1945.

14. Scharrer, E.: Capillaries and Mitochondria in Neuropil, J. Comp. Neurol. **83**:237, 1945.

15. Campbell, A. C. P.: Variation in Vascularity and Oxidase Content in Different Regions of the Brain of the Cat, Arch. Neurol. & Psychiat. **41**:223 (Feb.) 1939.

content in the brain is high where capillaries are densely clustered. Since mitochondria are carriers of respiratory enzymes the observations are all the more significant. Moreover, the brain has variations in blood flow which correspond to the active and quiescent areas. For example, there is increased flow in the occipital areas when the eyes are being used and in the olfactory bulb when a strong smell is being inhaled. This has been shown by a number of investigators.[16] Before the oxygen consumption of the brain is really well understood, there must be more studies of this local action. At present there is only proof that such action occurs in the occipital and parietal areas of the cortex, in the olfactory bulb and in the medulla.

McCulloch [17] and his co-workers have studied localized areas in the cortex of living animals for changes in p_H, lactic acid content and oxygen tension. The method of determining oxygen tension by electrical means in vivo was first employed by Bronk in the Johnson Foundation Laboratory at the University of Pennsylvania. McCulloch, at Illinois, has modified the method and applied it to the cortex of the cat, to see what changes occurred when the animal breathed nitrogen, when the cerebral blood flow was increased and when flow was reduced. Inhalation of nitrogen produced a precipitous fall in cortical oxygen tension. Decreasing blood flow caused a fall and increased blood flow a rise in oxygen tension. Breathing oxygen instead of air increases the tension in the cortex by 75 per cent, but this does not seem to affect the oxygen consumption of the cortex because the electrical activity of the cortex is not affected.

It has long been known that the energy of the brain is the result of a special type of metabolism; i. e., the brain derives its energy entirely from the combustion of dextrose, while most tissues burn either carbohydrates or ketones. The brain does not need insulin for the utilization of the pituitary diabetogenic hormone.[18] The work of Caspersson [19]

16. Schmidt, C. F., and Hendrix, J. P.: Action of Chemical Substances on Cerebral Blood-Vessels, A. Research Nerv. & Ment. Dis., Proc. (1937) **18**:229, 1938. Gerard, R. W.: Brain Metabolism and Circulation, ibid. **18**:316, 1938. Cobb, S., and Talbott, J. H.: Studies in Cerebral Circulation: Quantitative Study of Cerebral Capillaries, Tr. A. Am. Physicians **42**:255, 1927.

17. Roseman, E.; Goodwin, C. W., and McCulloch, W. S.: Rapid Changes in Cerebral Oxygen Tension Induced by Altering the Oxygenation and Circulation of the Blood, J. Neurophysiol. **9**:33, 1946.

18. Price, W. H.; Cori, C. F., and Colowick, S. P.: Effect of Anterior Pituitary Extract and of Insulin on the Hexokinase Reaction, J. Biol. Chem. **160**:633, 1945.

19. Caspersson, T.: Studies on Protein Metabolism in the Cells of Epithelial Tumors, Stockholm, P. A. Norstedt & Söner, 1942; On the Role of the Nucleic Acids in the Cell, in Proceedings of the Seventh International Genetical Congress, 1939, London, Cambridge University Press, 1941, p. 85.

has shown that there are various other metabolic activities in the brain, such as changes in the nucleoproteids when the nerve cells become active. These metabolic changes, however, are small and require extremely small amounts of energy, so that in general the statement may be made that the brain derives its energy from dextrose. The changes in the nucleoproteids described by Caspersson are, nevertheless, of great interest and show that changes take place in the active nerve cell rapidly and are reversible with cessation of this activity. They show that the proteids act differently within the nucleus and outside of it. Obviously more experiments are needed to study these chemical changes, and new methods are being developed which bring out the microchemical activities of the neurons.

THE BARRIER

Among the unique characteristics of the brain mentioned by Folch was the blood-brain barrier. This has been known to exist for a long time, because certain stains and toxins were observed which did not enter the brain from the blood. There must be, in fact, not only a blood-brain barrier, but a blood–spinal fluid barrier, which would lie in the choroid plexus, and a spinal fluid–brain barrier, which would be the pia and the lining of the perivascular spaces. Thus from the histologic point of view there is a barrier which must come down to something similar in structure to a capillary wall. Such a wall, however, is not sufficient to explain the action as a barrier, and one has to resort to chemistry. By using isotopic tracers it has been found that such substances as potassium, choline, lactic acid and pyruvic acid spread into the brain substance at a much slower rate than they diffuse into other tissues. This is probably due to the positive or negative charges on these ions, as explained by Friedemann.[20] Although much remains to be learned about the actual mechanism, there is no doubt that much of the "barrier" is caused by the chemical and osmotic relationships of the tissues on each side of the wall. Such relationships are probably more important in causing the barrier than the structure of the wall itself.

Kalz, Friedman, Schenker and Fischer[21] by an investigation of "false positive" Wassermann reactions came to the conclusion that reagin passes more easily from the serum to the spinal fluid in infants and in syphilitic patients than in normal controls. It has long been known that in newborn animals many substances pass freely from blood to spinal fluid which later in life are prevented from passing the barrier. Few observations have been made on human subjects. Kalz and his

20. Friedemann, U.: Blood-Brain Barrier, Physiol. Rev. **22**:125, 1942.

21. Kalz, F.; Friedman, H.; Schenker, A., and Fischer, I.: Permeability of Blood-Spinal Fluid Barrier in Infants and in Normal and Syphilitic Adults, Arch. Neurol. & Psychiat. **56**:55 (July) 1946.

colleagues determined the permeability of the barrier by Walter's bromide method. The bromide content of the blood is divided by the bromide content of the spinal fluid to give the "bromide permeability quotient." In 22 normal infants this was found to be between 1.21 and 3.39, with the mean near 2. In normal adults the range was from 2.1 to 3.9, with the mean at about 3. For adults with active neurosyphilis they found a range from 0.09 to 2.89, with the mean at 2.03. These results indicate that in infancy and in active infection of the central nervous system the permeability of the barrier is so changed that molecules of the size of those of reagin can easily pass through from blood to spinal fluid. In adults with normal meninges and ependyma and vessels such molecules cannot pass. This not only explains the "false-positive" Wassermann reactions but gives an excellent example of the action of the "barrier" in man.

CAUSALGIA

In this war the causalgia syndrome has developed in from 2 to 3 per cent of men suffering from penetrating wounds affecting the nerves of an extremity. The commonest site is the median nerve. The symptoms are well known from the wounded of former wars and occasional civil cases. There is burning pain in the sensory distribution of the injured nerve. This pain is constant and severe; it is made excruciating by touching or even by currents of air. Psychic disturbances bring on exacerbations. The victim becomes a recluse, nursing his limb and keeping away from stimuli. Trophic changes occur in the skin; it becomes shiny and smooth. The subcutaneous tissues and bones may show atrophy. There is considerable sweating and vasomotor change. Little relief has been given by curing local infection, freeing the nerve from adhesions, section of posterior roots and periarterial sympathectomy. Recently sympathetic denervation of the arm or leg has been found to be remarkably successful.[22] It appears that elimination of the efferent sympathetic discharge to the painful limb stops the pain. The implications of this surgical result are interesting.

Clinically it can be shown that the burning pain of causalgia occurs in direct relationship to the tonic vasomotor, sudomotor and pilomotor discharge over the sympathetic efferent pathways.[23] Cold or excessive heat, loud noises, jars, any excitement or emotional tension and hypodermic injections in any part of the body set up burning and sweating in the affected area. Indeed those factors that usually set up sympathetic discharge cause pain. On the other hand, blocking the sympathetic

22. White, J. C.: Painful Injuries of Nerves and Their Surgical Treatment, Am. J. Surg. **72**:468, 1946. Rasmussen, T. B., and Freedman, H.: Treatment of Causalgia: Analysis of One Hundred Cases, J. Neurosurg. **3**:165, 1946.

23. White, J. C.: Read before the Harvey Cushing Society, Oct. 13, 1946.

efferent discharge with tetraethyl ammonium bromide [24] or a warm quiet room or sleep causes the pain to stop. Mitchell in his original essay on the subject said: "I have heard men remark that it took some time to get awake to the pain."

The best theory to explain all this is that efferent nervous discharge along sympathetic fibers in a nerve can cause direct cross stimulation of the poorly myelinated afferent pain fibers near the point of injury.[25] Experimental evidence of Katz and Schmitt [26] that efferent nerve impulses can alter the excitability of adjacent afferent axons makes this theory probable. Furthermore, Granit, Leksell and Skoglund [27] have shown that such cross stimulation between motor and sensory neurons does take place. They recorded with a cathode ray oscillograph afferent discharges from the sensory root when the motor root was stimulated after partial injury to the nerve trunk in the periphery.

From the practical standpoint this means that in order to cure the pain of causalgia either the environment must be so restricted that no sympathetic discharge occurs in the patient's nervous system or sympathetic pathways to the affected limb must be interrupted. The former method led to chronic invalidism and frequently to suicide. The surgical operation of sympathectomy for a limb has now been so well perfected that the cure of this postwar torture for many wounded men is practically assured.

DERMATOMES AND RESISTANCE OF THE SKIN

The distribution of the sympathetic nerves to the skin was not well understood until Richter [28] published his important researches on the resistance of the skin of monkeys with experimental nerve block and on man in cases of injury of peripheral nerves and sympathectomy. The main facts are as follows:

(1) The resistance offered to the passage of a minute, imperceptible, direct current through the body is localized almost entirely in the skin. . . .

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24. Berry, R. L., and others: Use of Tetraethylammonium in Peripheral Vascular Disease and Causalgic States, Surgery **20**:525, 1946.

25. Doupe, J.; Cullen, C. H., and Chance, G. Q.: Post-Traumatic Pain and Causalgic Syndrome, J. Neurol., Neurosurg. & Psychiat. **7**:33, 1944.

26. Katz, B., and Schmitt, O. H.: Electric Interaction Between Two Adjacent Nerve Fibres, J. Physiol. **97**:471, 1940.

27. Granit, R.; Leksell, L., and Skoglund, C. R.: Fibre Interaction in Injured or Compressed Region of Nerve, Brain **67**:125, 1944.

28. Richter, C. P.: Instructions for Using the Cutaneous Resistance Recorder, or Dermometer, on Peripheral Nerve Injuries, Sympathectomies, and Paravertebral Blocks, J. Neurosurg. **3**:181, 1946. Bruesch, S. R., and Richter, C. P.: Cutaneous Distribution of Peripheral Nerves in Rhesus Monkeys as Determined by the Electrical Skin Resistance Method, Bull. Johns Hopkins Hosp. **78**:235, 1946. Richter, C. P., and Woodruff, B. G.: Lumbar Sympathetic Dermatomes in Man Determined by the Electrical Skin Resistance Method, J. Neurophysiol. **8**:323, 1945.

(2) Skin resistance is controlled largely through the nervous system. Thus, section of a peripheral nerve trunk produces a great and permanent increase in the resistance of the skin supplied by that nerve, while stimulation or irritation of the nerve has the opposite effect, producing a decrease in the skin resistance.

(3) Skin resistance depends on the sympathetic component of the peripheral nerves. Thus, it has been shown that: (a) Elimination of the sympathetic supply by ganglionectomy, while leaving the motor and sensory fibers intact, produces an increase in skin resistance as great as that produced by section of the entire nerve trunk. . . . (c) Factors stimulating the sympathetic nervous system, such as external heat, muscular effort, emotional excitement, or mental tension, tend to decrease skin resistance. The opposite is true of factors decreasing sympathetic activity, such as rest, sleep, relaxation, and freedom from mental tension. These act to increase skin resistance.

(4) Skin resistance varies directly with sweat gland activity, becoming low when the sweat glands are active and high when they are inactive.

The practical application of this knowledge is by means of an instrument devised by Richter and called a dermometer. Jasper [29] has modified this instrument and calls it a "dermohmmeter." This not only maps out accurately the areas where sympathectomy has deprived the skin of sympathetic innervation, but incidentally is a most accurate and objective way of checking on the areas of anesthesia caused by lesions of peripheral nerves. Ordinary clinical methods depend on the answers of the patient in response to stimuli. The "dermometer" gives a simple, objective method that can be applied to a child, a monkey, a malingerer or a patient in coma.

At the St. Albans Naval Hospital and the New York Neurological Institute cooperative research was carried out by Herz, Glaser, Moldaver and Hoen,[30] who studied a larger group of injuries of peripheral nerves, 87 cases of injury of individual nerves and 15 of injury of plexuses. They found that where there was complete sensory loss the area where the resistance of the skin was elevated corresponded almost exactly in 47 out of 51 cases. This demonstrates the value of the "dermohmmeter" in mapping out anesthetic areas. The results of mapping out areas of hypesthesia were less satisfactory. In only 13 out of 40 cases was there good correlation between the areas of partial sensory loss and heightened cutaneous resistance. In 16 cases there was no change in the resistance of the skin. It may be that in these cases the sympathetic nerves regenerated before the sensory nerves. This is a plausible explanation because the regenerative powers of the autonomic system are known to be great.

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29. Jasper, H. H.: Improved Clinical Dermohmmeter, J. Neurosurg. **2**:257. 1945.

30. Herz, E.; Glaser, G. H.; Moldaver, J., and Hoen, T. I.: Electrical Skin Resistance Test in Evaluation of Peripheral Nerve Injuries, Arch. Neurol. & Psychiat. **56**:365 (Oct.) 1946.

ELECTRIC SHOCK THERAPY

Practically all psychiatrists now agree that electric shock is of value in the affective psychoses.[31] It is probably most beneficial in the involutional depressions, over 80 per cent being conspicuously improved. This is important in a condition in which without treatment protracted depression was the rule, sometimes lasting for years. In manic-depressive patients, especially in the depressed phase, there is also about 80 per cent recovery after electric shock, but it must be remembered that the attacks of this disease are self limited and that if the patients were left untreated 80 to 90 per cent would recover spontaneously. The risk of suicide, however, is great, and shock treatment will save a certain number of patients who would kill themselves if left alone.[32] Moreover, the shock treatment shortens the depressions and saves the patient many weeks or months of unhappiness. In schizophrenia electric shock is largely of use as a symptomatic treatment to quiet disturbed patients. Many schizophrenic patients have appeared to improve after courses of electric shock, but most of them later relapse.

The long courses of treatment, fifty or more shocks, producing profound organic sensorial defects equivalent to an amentia[33] seem hardly justifiable. Many patients seem to be able to stand repeated shocks but others show pronounced deterioration after long courses. Brody[34] reported 6 cases of prolonged impairment of memory leading to disability. A brief loss of memory occurs after each shock, and a defect may be present for days or weeks after a course of eight or ten treatments. It is only after repeated courses of treatment that the loss seems to be prolonged or permanent. On the other hand, patients have failed to show deterioration after as many as 248 electroconvulsive shocks.[35]

Such conflicting observations make one wonder just what goes on in the brain when electric currents strong enough to cause convulsions are passed through the frontal lobes. Many experimental studies have been made. In the laboratories of ten different experimenters animals have been given convulsive shocks and the brains afterward examined. Five reported cerebral lesions and five said that there were no lesions

31. Solomon, H.: Shock Therapies in Psychiatry, Clinics **4**:555, 1945.

32. Ziskind, E.; Somerfeld-Ziskind, E., and Ziskind, L.: Metrazol and Electric Convulsive Therapy of the Affective Psychoses: A Controlled Series of Observations Covering a Period of Five Years, Arch. Neurol. & Psychiat. **53**:212 (March) 1945.

33. Bennett, A. E.: Evaluation of Electric Shock Therapies, Psychiatric Quart. **19**:465, 1945.

34. Brody, M. B.: Prolonged Memory Defects Following Electro-Therapy, J. Ment. Sc. **90**:777, 1944.

35. Perlson, J.: Psychologic Studies on a Patient Who Received Two Hundred and Forty-Eight Shock Treatments, Arch. Neurol. & Psychiat. **54**:409 (Dec.) 1945.

or that the lesions were not significant. Most of the experiments did not closely enough duplicate the conditions pertaining in human electroshock therapy to be important in answering the question. The most recent paper is the most convincing. Ferraro, Roizin and Helfand [36] used monkeys, observed them for months and used currents comparable to those used in therapy, taking into account the smaller size of the monkey brain. The 10 monkeys reported on in this paper received from four to eighteen convulsive shocks, an average number of ten each. All showed histologic changes in the brain. These were mostly in the frontal lobes, the part of the brain through which the current was passed. The commonest changes were in the nerve cells, which showed pyknosis, swelling and other changes. There were also swelling and proliferation of the glia. Capillary hemorrhages were common. The severity of the changes seemed to bear a relation to the intensity and duration of the current and to the number of electric shocks given. The authors believe that the changes in the nerve cells "are mostly the reversible type." This, however, is a matter of opinion. From the photographs in the paper one might consider some of the changes rather severe and likely to lead to cell death. It is probable, however, that man has a great many more nerve cells in his brain than he ever uses, so that many may be destroyed without causing permanent mental symptoms. In other words, there is a good margin of safety. Just how wide this margin actually is nobody at present can say.

A good review of the English experience with shock is given by Pullar-Strecker,[37] who sums up the situation well by saying:

> In Great Britain alone, E. C. T. [electrical convulsion therapy] has been applied to . . . about 10,000 patients of all ages up to 75. Six deaths were reported up to June 1944. [Complications occurring during or after treatment include:] (1) Dislocation of jaw and shoulder, fracture of humerus and femur, compression fracture of vertebra. . . . (2) Brain damage, such as impairment of the memory or intellectual deterioration. The latter is extremely rare, the former quite frequent, temporarily. . . . (3) Activation of old quiescent tuberculosis, . . . responsible for most of the deaths reported. (4) Undesirable mental sequelae, such as excitement, confusion, violence; aggravation of existing symptoms. . . . (5) Cardiovascular accidents. [These] no longer occur with reasonable selection of patients. (6) Activation of latent epilepsy.
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> . . . Absolute contra indications are recent tuberculosis, intracranial disorders, organic diseases of the central nervous system, and, temporarily, the presence of infection. . . .

36. Ferraro, A.; Roizin, L., and Helfand, M.: Morphologic Changes in the Brain of Monkeys Following Convulsions Electrically Induced, J. Neuropath. & Exper. Neurol. **5**:285, 1946.

37. Pullar-Strecker, H.: Scope of Electrical Convulsion Therapy, M. Press **214**:192, 1945.

[More often than not, electrical convulsion therapy reclaims the depressive.] The time factor, i.e., the duration of the illness, does not adversely affect results. . . . No more than 15 per cent of depressive patients remain unimproved by this treatment.

Other shock therapies are still being used. Metrazol convulsions, because of the fear reactions in the patients, are being used less and less. Insulin still holds an important place in the treatment of schizophrenia. In Russia [38] hemocolloidoclastic shock is being used successfully. Five or 10 cc. of incompatible blood is injected into a schizophrenic patient. There is immediately an acute disturbance of the vasomotor and vegetative functions with temperature as high as 40 C. (104 F.). In Khalurian's cases improvement occurred in 22 out of 35 cases. Galenko and Kirilova gave as much as 35 cc. of incompatible blood twice a week for a total of eight or ten injections. Among 22 cases of schizophrenia of short duration, considerable improvement occurred in 6 and some improvement in 9 more.

It is often stated that nothing is known of the mechanism by which shock therapy improves patients with psychotic symptoms. The microscopic observations on the pathologic changes in nerve cells certainly give one some conception of what is going on. Gellhorn's [39] physiologic experiments go further and indicate that the important factor may be the increased excitability of the sympathetic nervous system. Especially interesting are his experiments on rats which show that insulin coma and electrical convulsions can lead to a restoration of inhibited conditioned reactions. In discussing the hyperactivity of the sympathetic system he says:

Such effects may persist for considerable periods. It must therefore be assumed that discharges from these centers, particularly from the hypothalamus, are increased above the normal value. Murphy and Gellhorn showed recently that the sympathetic parts of the hypothalamus give rise to impulses afferent to the motor cortex, the primary sensory projection area and the association centers of the brain. These impulses increase the effectiveness of subthreshold stimulation of the motor cortex to such a degree that distinct movements may result. Furthermore, studies of the action potentials of the cortex have shown that under the influence of these hypothalamic impulses the cortical excitability is greatly increased and the number of active neurons enlarged. These data suggest that cortical residues of previously established conditioned reactions may be activated as a result of the heightened hypothalamic activity following insulin coma. This may account for the restoration of inhibited conditioned reactions.

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38. Khalurian, G. M.: Nevropat. i psikhiat. **14**:40, 1945. Galenko, V. E., and Kirilova, A. Z.: ibid. **14**:38, 1945.

39. Gellhorn, E.: Is Restoration of Inhibited Conditioned Reactions by Insulin Coma Specific for Pavlovian Inhibitions? Contribution to the Theory of Shock Treatment, Arch. Neurol. & Psychiat. **56**:216 (Aug.) 1946.

LESSONS FROM MILITARY PSYCHIATRY

General Menninger [40] has written an important paper, giving his opinion as to what important lessons were learned from the Army experience concerning psychiatry. His paper will be read by most psychiatrists, who know what a splendid job he did as chief of psychiatry in The Surgeon General's Office. The paper should be read by the dean of every medical school and by every professor of medicine. The war experience dispels once and for all the misconception that psychiatric disorders are "incurable" or do not respond well to treatment. With few and often briefly trained psychiatrists to treat the men with neurosis, 90 per cent were returned to duty overseas and of the 10 per cent sent back to this country between 25 and 50 per cent were salvaged. Even among those with psychotic reactions 70 per cent were able to return to their homes rather than to veterans' hospitals. If it is true that 50 per cent of all patients of all physicians in civil practice have symptoms on a neurotic basis, these figures indicate that a tremendous number of persons have a hopeful prognosis if treatment can be started early. But there's the rub. In the Army the patients were young men; they were under supervision and were sent to a physician as soon as symptoms appeared. In civil life it is exceptional for a patient to seek a psychiatrist in the early stages of his maladjustment. "The lesson would seem to be that psychiatry must aim first towards active, early treatment."

The person in war is exposed to fear, isolation, discomfort, privation and many other new difficulties which tend to disintegrate him. Factors which aided integration were found to be effective leadership, identification with a group, confidence gained from training and conviction as to the importance of the job. Seeing these factors at work on the morale of different groups of men emphasized to psychiatrists and all others who were observant that stress from social forces was a major factor in the causation of psychiatric casualties. This is not new, but it is the sort of thing which is uncritically taken for granted. Here are data.

Another important contribution toward the practical handling of neurotic patients was the way in which auxiliary personnel could be used. Clinical psychologists and psychiatric social workers can help a great deal in diagnosis and treatment. This of course must be supervised by the psychiatrist, and ideally the psychologic interviews should be in the hands of a psychiatrist, but in the face of the shortage of physicians who are interested in or trained in psychiatry it is only practical to make use of these nonmedical assistants. Many more psychiatrically

40. Menninger, W. C.: Lessons from Military Psychiatry for Civilian Psychiatry, Ment. Hyg. **30**:571, 1946.

trained nurses and occupational and educational therapists are also needed.

In treatment the three main contributions, according to Menninger, were:

> . . . the improvement of group psychotherapeutic methods, experience with psychotherapy under sedation, and the development of an elaborately organized program of activities for neurotic patients. None of these was essentially new, but each was greatly elaborated and a mass of new experience accumulated.
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> Group psychotherapy rose to prominence through expediency. It seemed to be the best method for the psychiatrist to spend some additional time with his patients. Following the adage that "necessity is the mother of invention," it became recognized as having many advantages not possible in individual psychotherapy. Most conspicuous of these was the sharing among the group of problems that the individual had assumed to be unique to himself. With the sharing came the finding of solutions in the contributions of other patient failures or successes. The social forces of group opinion, approval or disapproval, became one of group therapy's major advantages that was most effectively developed in the correction installations. This method of treatment seemed to be more effective in changing attitudes than in actually relieving symptoms, but the two can hardly be separated.
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> Psychotherapy under sedation was widely utilized . . . The experience gained would suggest that it is an extremely valuable short-cut method and that, if properly used and further developed, it might be one of the chief contributions of military psychiatry to civilian practice, as one type of abbreviated psychotherapy.
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> The third contribution to improved therapeutic technique was possible chiefly because of the almost inexhaustible resources expended by the army for the treatment of disabled soldiers. In the twelve convalescent hospitals of the army service forces and in a considerable number in the air force, an elaborate system was developed. The individual patient with a neurotic reaction was exposed, in consecutive series, to individual psychotherapy, group psychotherapy, and a battery of educational, occupational, and recreational opportunities, hardly available in even the most ideal civilian psychiatric-treatment center in the country.

News and Comment

FOURTH ANNUAL MEDICAL AND SURGICAL SYMPOSIUM

Sponsored by
THE WATTS HOSPITAL STAFF OF WATTS HOSPITAL
Durham, N. C.

Wednesday, February 12, 1947

11:00 A. M. Clinico-Pathological Conference, presented by Sidney **Farber,** M.D., Department of Pathology, Harvard Medical School, Boston, and Charles D. May, M.D., Associate in Pediatrics, Harvard Medical School, Boston

2:30 P. M. "Surgical Aspects of Diabetes," Leland S. McKittrick, M.D., Boston

3:30 P. M. "Recent Advances in the Study and Treatment of Diabetes," Howard F. Root, M.D., Boston

8:00 P. M. "Viral Hepatitis," Joseph Stokes Jr., M.D., Professor of Pediatrics, University of Pennsylvania Medical School, Philadelphia

9:00 P. M. "Pericardial Scars," Francis C. Wood, M.D., Assistant Professor of Medicine, University of Pennsylvania Medical School, Philadelphia

Thursday, February 13

11:00 A. M. Clinico-Pathological Conference, presented by J. E. Ash, Colonel, Medical Corps, Director, Army Institute of Pathology, Washington, D. C., and Wallace Yater, M.D., former Professor of Medicine at Georgetown University

2:30 P. M. "Some Clinical and Physiologic Aspects of Portal Cirrhosis," Albert M. Snell, M.D., Mayo Clinic, Rochester, Minn.

3:30 P. M. "The Current Status of Calcium Penicillin in Beeswax and Peanut Oil," Monroe J. Romansky, M.D., George Washington University School of Medicine, Washington, D. C.

8:00 P. M. "The Present Status of Effective Specific Therapy Based on Exact Hematologic Diagnosis," Charles A. Doan, M.D., Dean, College of Medicine, Ohio State University, Columbus, Ohio

ANNOUNCEMENTS

Research Fellowships in Medicine.—The American College of Physicians offers a limited number of research fellowships designed to provide an opportunity for research training in either the basic medical sciences or the application of the sciences to clinical investigation. The fellowships are for the benefit of physicians who are in the early stages for preparation for a teaching or investigative career in internal medicine, pediatrics and other allied fields. The term of appointment is for one year, usually beginning July 1. The stipend will be from $1,800 to $3,000 per annum. Application forms may be procured from the American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa. It is desirable that applications be filed by December 1 each year. Awards will be made on or about January 1.

Postgraduate Courses at the University of California.—The University of California Medical School, with the cooperative administration of University Extension, University of California, will shortly announce a program of postgraduate instruction to be offered at the Medical Center, San Francisco. A variety of courses will be given which will encompass the fields of internal medicine, general surgery, obstetrics and gynecology, otorhinolaryngology, ophthalmology, psychiatry and the basic sciences, as well as a course specially designed to meet the needs of general practitioners here mentioned.

Fees for all these courses will be covered by the provisions of the G. I. Bill of Rights.

A refresher course in internal medicine and general surgery, which will be given February 10 to 14, inclusive, 1947, at the University of California Hospital, Medical Center, San Francisco, is primarily designed for general practitioners. It will include the recent advances in diagnosis and treatment in internal medicine and general surgery. It is open only to graduates of approved medical schools. The fee for this course will be announced in a detailed notice mailed on request.

For further information with regard to these various programs of postgraduate instruction kindly communicate with Stacy R. Mettier, M.D., Head of Postgraduate Instruction, Medical Extension, University of California Medical Center, San Francisco 22, Calif.

Award for Essay on Result of Research in Urology.—The American Urological Association offers an annual award "not to exceed $500" for an essay (or essays) on the result of some clinical or laboratory research in urology. The offer is limited to urologists who have been in such specific practice for not more than five years and to residents in urology in recognized hospitals. Further information may be procured from the Secretary, Dr. Thomas D. Moore, 899 Madison Avenue, Memphis, Tenn.